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(54) Title: PURINE INHIBITORS OF CYCLIN DEPENDENT KINASE 2 AND Iκ–Aα

(57) Abstract

A 2,6,9–trisubstituted purine composition that is useful for inhibiting cell proliferative disorders and as an antifungal agent.

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Title: PURINE INHIBITORS OF CYCLIN DEPENDENT KINASE 2 and IκB-α

BACKGROUND OF THE INVENTION

This is a continuation-in-part of U.S. Patent Application S.N. 09/230,829, filed on January 29, 1999, which claims priority to PCT Application No. PCT/US97/13386, filed on August 1, 1997 which in turn is a continuation-in-part of co-pending U.S. Patent Application Serial No. 08/692,012 filed August 2, 1996.

(1) Field of the Invention

This invention concerns 2,6,9-trisubstituted purines that have been discovered to be selective inhibitors of cell cycle kinases and, as such, the compounds are inhibitors of cell proliferation. The 2,6,9-trisubstituted purines are useful in for example in - treating autoimmune diseases, e.g. rheumatoid arthritis, lupus, type I diabetes, multiple sclerosis, etc., in treating cancer, cardiovascular disease, such as restenosis, host vs graft disease, gout, polycystic kidney disease and other proliferative diseases whose pathogenesis involves abnormal cell proliferation.

This invention also concerns 2,6,9-trisubstituted purines that have been discovered to be potent and specific inhibitors of IκB-α kinase which prevents signal induced NF-κB activation and cytokine synthesis in vitro and in vivo. Such inhibitors are expected to inhibit the synthesis of cytokines and adhesion proteins whose synthesis is transcriptionally regulated by NF-κB. Proinflammatory cytokines such as lL-1, lL-6, TNF and adhesion proteins (e.g. ICAM, VCAM and selections) belong to this class of molecules and have been implicated in

the pathogenesis of inflammatory diseases. Thus a potent inhibitor of IκB-α kinase is useful in the clinical management of diseases where NF-κB activation is required for disease induction.

(2) Description of the Art

In the past few years, advances in molecular and cellular biology have contributed to our understanding of the mechanisms of cell proliferation and of specific events that occur during progression of cells through mitosis. *E.g.*, "Progress in Cell Cycle Research" Vol 1, Eds. L. Meijer, S. Guidet and H.Y.L. Tung; Plenum Press, New York, 1995. These studies have shown that progression through the cell cycle is controlled by a family of serine/threonine kinases called cyclin dependent kinases. These enzymes contain (a) a catalytic protein called cyclin dependent kinase (CDK) that uses ATP as a substrate and (b) a regulatory protein called cyclin. Different cyclin-CDK combinations control events such as growth, DNA replication and cell division. One key member of the CDK family of enzymes is CDK2. CDK2 activity has been shown to be essential for mammalian cell cycle progression at the G1/S boundary. Microinjection of antibodies directed against CDK2 blocks the progression of human diploid fibroblasts into the S phase of the cell cycle. Expression of a CDK2 dominant negative mutant in human osteosarcoma cells has a similar effect. Together, these studies indicate that inhibition of cellular CDK2 activity will prevent progression of cells through the mitotic cycle and induce growth arrest prior to the S phase. Consistent with this view, in vitro studies with olomoucine (2-(hydroxyethylamino)-6-benzylamino-9-methylpurine), have shown that it is a specific inhibitor of CDK2 with an IC_{50} of approximately 2.1 μg/ml J. Vesely, et al.; Eur. J.Biochem 224, 771-786 (1994), L. Meijer "Chemical Inhibitors of Cyclin-Dependent Kinases" pp 351-356 in "Progress in Cell Cycle

Research Vol 1, Eds. L. Meijer, S. Guidet and H.Y.L. Tung; Plenum Press, New York, 1995. In vivo studies using mammalian cells in culture have shown that olomoucine inhibits cell proliferation at an approximate concentration of 50 μg/ml.

In this invention, we have developed several compounds whose biological activity is considerably more potent than olomoucine. In vivo studies using mammalian cells indicate that some of the disclosed compounds inhibit cell proliferation at concentrations that are significantly lower than olomoucine.

Recently an IκB-α kinase activity has been described in the cytoplasm of stimulated human umbilical vein endothelial cells (Bennett et al (1996) J. Biol.Chem 271, 19680-19688). Some of the compounds of this invention have been identified as potent and specific inhibitors of IκB-α kinase which prevents signal induced NF-κB activation and cytokine synthesis in vitro and in vivo. The activation of the heterodimeric transcription factor NF-κB is a complex process. In unstimulated cells, the NF-κB (p50/p65) heterodimer is located in the cytosol where it is complexed with an inhibitory subunit IκB-α, IκB-α, binds to NF-κB thus masking its nuclear localization signal and preventing translocation to the nucleus. Upon stimulation of cells with a variety of signals (e.g. lipopolysaccharide) IκB-α is rapidly phosphorylated, uniquitinated and degraded by the proteasome. Degradation of IκB-α, allows the translocation of NF-κB to the nucleus where it activates transcription of a number of inflammatory response genes.

These observations suggest that IκB-α kinase is an attractive target for the identification of inhibitors that may be useful in the treatment of inflammatory diseases where NF-κB activation is required for disease induction.

SUMMARY OF THE INVENTION

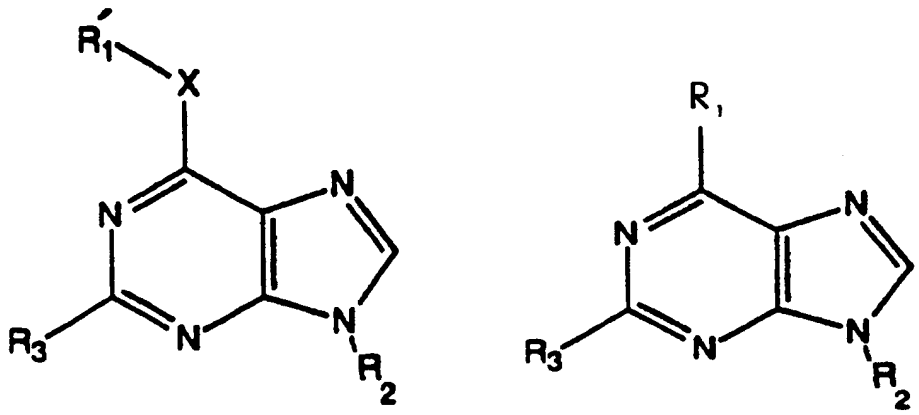
It is an object of this invention to provide 2,6,9-trisubstituted purine compounds, which inhibit the cyclin dependent kinase 2.

It is another object of this invention to provide 2,6,9-trisubstituted purine compounds which are useful for inhibiting cell proliferation.

This invention also constitutes a pharmaceutical composition, which comprises a 2,6,9-trisubstituted purine compound and a pharmaceutically acceptable carrier.

This invention further constitutes a method for inhibiting cell proliferation, which comprises administering to a mammal in need thereof an effective amount of a 2,6,9-trisubstituted purine compound.

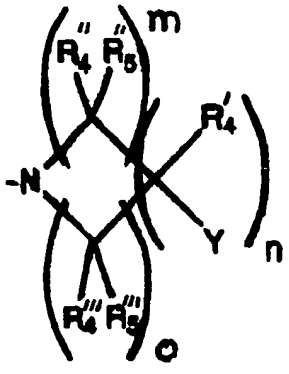
In one embodiment, this invention is A 2,6,9-trisubstituted purine composition of matter having the following formula:



(I)

wherein R_1 is halogen or R'_1-X wherein X = NH, O, S, $S(O_2)$. In the composition, R'_1 is alkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkenyl, and alkynyl, each

having one to 20 carbon atoms, which alkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkenyl, and alkynyl, are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, aryl, CF_3, heteroaryl, heterocyclyl, R^{22}, SR^{20}, $S(O)R^{21}$, SO_2R^{21}, $SO_2NR^{20}R^{23}$, $SO_2NR^{20}COR^{21}$, $SO_2NR^{20}CONR^{20}R^{23}$, $SO_2NR^{20}CO_2R^{21}$, $NR^{20}R^{23}$, $NR^{20}COR^{21}$, $NR^{20}CO_2R^{21}$, $NR^{20}CONR^{20}R^{23}$, $N(R^{20})C(NR^{20})NHR^{23}$, $NR^{20}SO_2R^{21}$, OR^{20}, $OCONR^{20}R^{23}$, $OCONR^{20}SO_2R^{21}$, $OCONR^{20}R^{23}$, CN, CO_2R^{20}, $CONR^{20}R^{23}$, $CONR^{20}SO_2R^{21}$ and COR^{20}. Also in the composition, R_2 is a hydrogen or hydrocarbon selected from the group alkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkenyl,and alkynyl, each having one to 20 carbon atoms, which alkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkenyl,and alkynyl,are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, aryl, heteroaryl, heterocyclyl, R^{22}, SR^{20}, $S(O)R^{21}$, SO_2R^{21}, $SO_2NR^{20}R^{23}$, $SO_2NR^{20}COR^{21}$, $SO_2NR^{20}CONR^{20}R^{23}$, $SO_2NR^{20}CO_2R^{21}$, $NR^{20}R^{23}$, $NR^{20}COR^{21}$, $NR^{20}CO_2R^{21}$, $NR^{20}CONR^{20}R^{23}$, $N(R^{20})C(NR^{20})NHR^{23}$, $NR^{20}SO_2R^{21}$, OR^{20}, $OCONR^{20}R^{23}$, $OCONR^{20}SO_2R^{21}$, $OCONR^{20}R^{23}$, CN, CO_2R^{20}, $CONR^{20}R^{23}$, $CONR^{20}SO_2R^{21}$ and COR^{20}. Further, in the compositions, R_3 is a halogen, hydroxyl, thio, alkoxy, alkylthio, alkyl, $-NR_4R_5$ or a component having the formula:



where m=1-3, n=1-3, o=1,3, y=carbonyl, -NR_4R_5, hydroxyl, thiol, alkoxy, alkylthiol;

R_4 and R_5 are each independently hydrogen, OR_{20}, $NR_{20}R_{23}$, or a hydrocarbon selected from the group including alkyl, acyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkenyl,and alkynyl, each having one to 20 carbon atoms, which alkyl, acyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkenyl,and alkynyl,are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, aryl, heteroaryl, heterocyclyl, R^{22}, SR^{20}, $S(O)R^{21}$, SO_2R^{21}, $SO_2NR^{20}R^{23}$, $SO_2NR^{20}COR^{21}$, $SO_2NR^{20}CONR^{20}R^{23}$, $SO_2NR^{20}CO_2R^{21}$, $NR^{20}R^{23}$, $NR^{20}COR^{21}$, $NR^{20}CO_2R^{21}$, $NR^{20}CONR^{20}R^{23}$, $N(R^{20})C(NR^{20})NHR^{23}$, $NR^{20}SO_2R^{21}$, OR^{20}, $OCONR^{20}R^{23}$, $OCONR^{20}SO_2R^{21}$, $OCONR^{20}R^{23}$, CN, CO_2R^{20}, $CONR^{20}R^{23}$, $CONR^{20}SO_2R^{21}$ and COR^{20};

R^{20} is a member selected from the group consisting of H, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl, and heteroaryl, which alkyl, alkenyl, alkynyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from halo, alkyl, mono- or dialkylamino, alkyl or aryl or heteroaryl amide, CN, O-C_{1-6} alkyl, CF_3, aryl, and heteroaryl;

R^{21} is a member selected from the group consisting of C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl, and heteroaryl, which alkyl, alkenyl, alkynyl, aryl, heterocyclyl, and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from the group of halo, heterocyclyl, aryl, heteroaryl, CF_3, CN, OR^{20}, SR^{20}, $N(R^{20})_2$, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, $SO_2NR^{20}COR^{22}$, $SO_2NR^{20}CO_2R^{22}$, $SO_2NR^{20}CON(R^{20})_2$, $N(R^{20})_2$ $NR^{20}COR^{22}$, $NR^{20}CO_2R^{22}$, $NR^{20}CON(R^{20})_2$, $NR^{20}C(NR^{20})NHR^{23}$, COR^{20}, CO_2R^{20}, $CON(R^{20})_2$, $CONR^{20}SO_2R^{22}$, $NR^{20}SO_2R^{22}$, $SO_2NR^{20}CO_2R^{22}$, OR^{20}, $OCONR^{20}SO_2R^{22}$, $OC(O)R^{20}$, $C(O)OCH_2OC(O)R^{20}$, and $OCON(R^{20})_2$, and each optional heteroaryl, aryl, and heterocyclyl

substituent is optionally substituted with halo, alkyl, CF_3, amino, mono- or di- alkylamino, alkyl or aryl or heteroaryl amide, $NCOR^{22}$, $NR^{20}SO_2R^{22}$, COR^{20}, CO_2R^{20}, $CON(R^{20})_2$, $NR^{20}CON(R^{20})_2$, $OC(O)R^{20}$, $OC(O)N(R^{20})_2$, SR^{20}, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, CN, or OR^{20};

R^{22} is a member selected from the group consisting of C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl, and heteroaryl, which alkyl, alkenyl, alkynyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from halo, alkyl, mono- or dialkylamino, alkyl or aryl or heteroaryl amide, CN, O-C_{1-6} alkyl, CF_3, aryl, and heteroaryl; and

R^{23} is R^{21} or H.

There are some limitations to the scope of the compositions of this invention. When Y is carbonyl, Y and R'$_4$ together may be a single oxygen atom, R_4" and R_5" together may be a single oxygen atom, R_4"' and R_5"' may together be a single oxygen atom. When R_3 is 2-hydroxyethylamino and R_2 is methyl, R_1'-X is not amino, 3-methyl-2-butenylamino, benzylamino, or m-hydroxybenzylamino when R_3 is not 2-hydroxyethylamino. When R_2 is isopropyl, R_1'-X is not benzylamino, m-hydroxybenzylamino, or 3-methylbutylamino. When R_3 is 2-hydroxyethylamino and R_2 is 2-hydroxyethyl, R_1'-X is not benzylamino and when R_3 is selected from the group consisting of 2-methyl-2-hydroxypropylamino, and 2-dimethylaminoethylamino, and when R_2 is methyl, then R_1'-X is not benzylamino

In another embodiment, this invention is a method for inhibiting cell proliferation in mammals comprising administering a therapeutically effective amount of the composition of claim 1 to the mammal. The method is useful for treating cell proliferation disorders such as rheumatoid arthritis, lupus, type I diabetes, multiple sclerosis, cancer, restenosis, host graft disease, and gout.

In yet another embodiment, this invention is a pharmaceutical composition of matter comprising the composition above in an admixture with one or more pharmaceutical excipients.

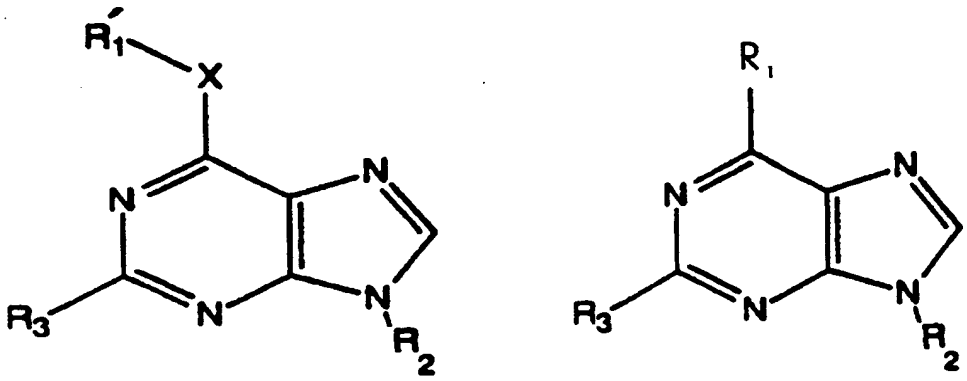
In still another embodiment, this invention is a composition useful for treating fungal infections (fungi) in humans, animals, and in plants.

DESCRIPTION OF THE FIGURE

Figure 1 is a plot of the mean neointimal area of a rat carotid artery treated with a saline vehicle and treated with compound 3 prepared according to Example 2 wherein the unshaded bar represents the untreated section of the carotid artery and the shaded bar represents the treated section of the carotid artery.

DESCRIPTION OF THE CURRENT EMBODIMENT

The present invention relates to a 2,6,9-trisubstituted purine compound having the following formulas:



(I)

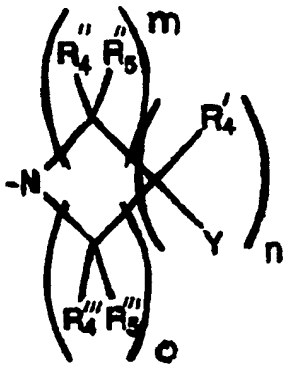
where:

R_1 is halogen or R'_1-X wherein X = NH, O, S, $S(O_2)$.

R'_1 is alkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkenyl, and alkynyl, each having one to 20 carbon atoms, which alkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkenyl, and alkynyl, are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, aryl, CF_3, heteroaryl, heterocyclyl, R^{22}, SR^{20}, $S(O)R^{21}$, SO_2R^{21}, $SO_2NR^{20}R^{23}$, $SO_2NR^{20}COR^{21}$, $SO_2NR^{20}CONR^{20}R^{23}$, $SO_2NR^{20}CO_2R^{21}$, $NR^{20}R^{23}$, $NR^{20}COR^{21}$, $NR^{20}CO_2R^{21}$, $NR^{20}CONR^{20}R^{23}$, $N(R^{20})C(NR^{20})NHR^{23}$, $NR^{20}SO_2R^{21}$, OR^{20}, $OCONR^{20}R^{23}$, $OCONR^{20}SO_2R^{21}$, $OCONR^{20}R^{23}$, CN, CO_2R^{20}, $CONR^{20}R^{23}$, $CONR^{20}SO_2R^{21}$ and COR^{20};

R_2 is a hydrogen or hydrocarbon selected from the group alkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkenyl,and alkynyl, each having one to 20 carbon atoms, which alkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkenyl,and alkynyl,are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, aryl, heteroaryl, heterocyclyl, R^{22}, SR^{20}, $S(O)R^{21}$, SO_2R^{21}, $SO_2NR^{20}R^{23}$, $SO_2NR^{20}COR^{21}$, $SO_2NR^{20}CONR^{20}R^{23}$, $SO_2NR^{20}CO_2R^{21}$, $NR^{20}R^{23}$, $NR^{20}COR^{21}$, $NR^{20}CO_2R^{21}$, $NR^{20}CONR^{20}R^{23}$, $N(R^{20})C(NR^{20})NHR^{23}$, $NR^{20}SO_2R^{21}$, OR^{20}, $OCONR^{20}R^{23}$, $OCONR^{20}SO_2R^{21}$, $OCONR^{20}R^{23}$, CN, CO_2R^{20}, $CONR^{20}R^{23}$, $CONR^{20}SO_2R^{21}$ and COR^{20};

R_3 is a halogen, hydroxyl, thio, alkoxy, alkylthio, alkyl, $-NR_4R_5$ or a component having the formula:



where m=1-3, n=1-3, o=1,3, y=carbonyl, $-NR_4R_5$, hydroxyl, thiol, alkoxy, alkylthiol;

R_4 and R_5 are each independently hydrogen, OR_{20}, $NR_{20}R_{23}$, or a hydrocarbon selected from the group including alkyl, acyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkenyl,and alkynyl, each having one to 20 carbon atoms, which alkyl, acyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkenyl,and alkynyl,are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, aryl,

heteroaryl, heterocyclyl, R^{22}, SR^{20}, $S(O)R^{21}$, SO_2R^{21}, $SO_2NR^{20}R^{23}$, $SO_2NR^{20}COR^{21}$, $SO_2NR^{20}CONR^{20}R^{23}$, $SO_2NR^{20}CO_2R^{21}$, $NR^{20}R^{23}$, $NR^{20}COR^{21}$, $NR^{20}CO_2R^{21}$, $NR^{20}CONR^{20}R^{23}$, $N(R^{20})C(NR^{20})NHR^{23}$, $NR^{20}SO_2R^{21}$, OR^{20}, $OCONR^{20}R^{23}$, $OCONR^{20}SO_2R^{21}$, $OCONR^{20}R^{23}$, CN, CO_2R^{20}, $CONR^{20}R^{23}$, $CONR^{20}SO_2R^{21}$ and COR^{20}; with the proviso that when Y is carbonyl, Y and R'_4 together may be a single oxygen atom, R_4" and R_5" together may be a single oxygen atom, R_4"' and R_5"' may together be a single oxygen atom, and wherein when R_3 is 2-hydroxyethylamino and R_2 is methyl, R_1'-X is not amino, 3-methyl-2-butenylamino, benzylamino, or m-hydroxybenzylamino, when R_3 is not 2-hydroxyethylamino, when R_2 is isopropyl, R_1'-X is not benzylamino, m-hydroxybenzylamino, or 3-methylbutylamino, when R_3 is 2-hydroxyethylamino and R_2 is 2-hydroxyethyl, R_1'-X is not benzylamino and when R_3 is selected from the group consisting of 2-methyl-2-hydroxypropylamino, and 2-dimethylaminoethylamino, and when R_2 is methyl, then R_1'-X is not benzylamino.

In the compositions, R^{20} is a member selected from the group consisting of H, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl, and heteroaryl, which alkyl, alkenyl, alkynyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from halo, alkyl, mono- or dialkylamino, alkyl or aryl or heteroaryl amide, CN, O-C_{1-6} alkyl, CF_3, aryl, and heteroaryl.

Also in the compositions, R^{21} is a member selected from the group consisting of C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl, and heteroaryl, which alkyl, alkenyl, alkynyl, aryl, heterocyclyl, and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from the group of halo, heterocyclyl, aryl, heteroaryl, CF_3, CN, OR^{20}, SR^{20}, $N(R^{20})_2$, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, $SO_2NR^{20}COR^{22}$, $SO_2NR^{20}CO_2R^{22}$, $SO_2NR^{20}CON(R^{20})_2$, $N(R^{20})_2$ $NR^{20}COR^{22}$, $NR^{20}CO_2R^{22}$, $NR^{20}CON(R^{20})_2$, $NR^{20}C(NR^{20})NHR^{23}$,

COR^{20}, CO_2R^{20}, $CON(R^{20})_2$, $CONR^{20}SO_2R^{22}$, $NR^{20}SO_2R^{22}$, $SO_2NR^{20}CO_2R^{22}$, OR^{20}, $OCONR^{20}SO_2R^{22}$, $OC(O)R^{20}$, $C(O)OCH_2OC(O)R^{20}$, and $OCON(R^{20})_2$, and each optional heteroaryl, aryl, and heterocyclyl substituent is optionally substituted with halo, alkyl, CF_3, amino, mono- or di- alkylamino, alkyl or aryl or heteroaryl amide, $NCOR^{22}$, $NR^{20}SO_2R^{22}$, COR^{20}, CO_2R^{20}, $CON(R^{20})_2$, $NR^{20}CON(R^{20})_2$, $OC(O)R^{20}$, $OC(O)N(R^{20})_2$, SR^{20}, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, CN, or OR^{20}.

In the compositions, R^{22} is a member selected from the group consisting of $C_{1\text{-}15}$ alkyl, $C_{2\text{-}15}$ alkenyl, $C_{2\text{-}15}$ alkynyl, heterocyclyl, aryl, and heteroaryl, which alkyl, alkenyl, alkynyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from halo, alkyl, mono- or dialkylamino, alkyl or aryl or heteroaryl amide, CN, O-$C_{1\text{-}6}$ alkyl, CF_3, aryl, and heteroaryl, and R^{23} is R^{21} or H.

R'_1 is preferably an aryl, substituted aryl, each having 6 carbon atoms wherein substitution includes optional substitution with from 1 to 2 substituents independently selected from the group consisting of halo, CF_3, aryl, R^{22}, $NR^{20}R^{23}$, $NR^{20}COR^{21}$, OR^{20}, CN; an aralkyl, substituted aralkyl, each having 6-8 carbon atoms wherein substitution includes optional substitution with from 1 to 2 substituents independently selected from the group consisting of halo, CF_3, aryl, R^{22}, $NR^{20}R^{23}$, $NR^{20}COR^{21}$, OR^{20}, CN; $-CH_2-$phenyl wherein the phenyl ring is optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, CF_3, R^{22}, OR^{20}, CN; substituted pyridylalkyl; unsubstituted pyridylalkyl; pyridyl; substituted pyridyl; and benzyl substituted with a halogen, alkoxy, phenyl, pyridyl or nitro group. In some compositions, R'_1 is preferably CH_2 - aryl or CH_2 - substituted aryl. Most preferably, R_1' is selected from 3-methylthiophenyl, 4-methylthiophenyl, 4-phenylbenzyl, 4-methoxybenzyl, 4-biphenyl, 3-methoxybenzyl, 4-(2-

thienyl)benzyl, 4-(4-methyl)phenylbenzyl, 4-(4-trifluoromethyl)phenylbenzyl, 4-(4-nitrilo)phenylbenzyl, 4-(2-pyridinyl)benzyl, piperonyl, 3-methoxbenzyl, 4-chlorobenzyl, and 4-nitrobenzyl.

R_2 is preferably hydrogen or a hydrocarbon selected from the group substituted lower alkyl, cycloalkyl, substituted cycloalkyl each having one to 6 carbon atoms wherein substitution includes optional substitution with from 1 to 2 substituents independently selected from the group consisting of halo, R^{22}, $NR^{20}R^{23}$, OR^{20}; substituted alkyl, cycloalkyl, substituted cycloalkyl each having one to 6 carbon atoms wherein substitution includes optional substitution with from 1 to 2 substituents independently selected from the group consisting of halo, R^{22}, $NR^{20}R^{23}$, and OR^{20}. More preferably, R_2 is isopropyl.

R_3 is preferably $-NR_4R_5$ wherein R_4 and R_5 are each selected from the group consisting of hydrogen, alkyl, heterocyclyl, acyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkyl alkenyl, alkyl alkynyl, each having one to 20 carbon atoms, which alkyl, acyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl,are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, aryl, heteroaryl,heterocyclyl, R^{22}, SR^{20}, $S(O)R^{21}$, SO_2R^{21}, $SO_2NR^{20}R^{23}$, $NR^{20}R^{23}$, $NR^{20}COR^{21}$, $NR^{20}CO_2R^{21}$, $NR^{20}CONR^{20}R^{23}$, $NR^{20}SO_2R^{21}$, OR^{20}, CN, CO_2R^{20}, $CONR^{20}R^{23}$, and COR_{20}. In some compositions, R_4 and R_5 are preferably each H, $-CH_2CH_2OH$, $-CHR'CH_2OH$, or $-CH_2CHR'OH$, $-CH_2CH_2NH_2$, $CHR'CH_2NH_2$, $-CH_2CHR'NH_2$ wherein R' is hydrogen or alkyl having from 1 to 6 carbon atoms.

R^{20} is preferably a member selected from the group consisting of H, $C_{1\text{-}8}$alkyl.

R^{21} is preferably a member selected from the group consisting of C_{1-3} alkyl, which alkyl is optionally substituted with 1 to 2 substituents independently selected from the group of halo, CF_3, CN, OR^{20}, SR^{20}, $N(R^{20})_2$.

R^{22} is preferably a member selected from the group consisting of C_{1-3}alkyl, aryl, heteroaryl which alkyl, aryl, and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from halo, alkyl, mono- or dialkylamino, alkyl or aryl, CN, O-C_{1-6} alkyl, and CF_3.

Preferred 2,6,9-trisubstuted purine compositions of this invention include 2-{(2-hydroxyethyl)[9-(methylethyl)-6-({[4-(trifluoromethyl)phenyl]methyl}amino)purin-2-yl]amino}ethan-1-ol, {((2S)oxolan-2-yl)methyl](6-{[(4-fluorophenyl)methyl]amino}-9-(methylethyl)purin-2-yl)amine, [((2R)oxolan-2-yl)methyl](6-{[(4-fluorophenyl)methyl]amino}-9-(methylethyl)purin-2-yl)amine, (2-aminoethyl)(6-{[3,5-dichlorophenyl)methyl]amino}-9-(methylethyl)purin-2-yl)amine, (2-aminoethyl)[6-({[4-chloro-3-(trifluoromethyl)phenyl]methyl}amino)-9-(methylethyl)purin-2-yl]amine, [-[(6-{[(4-chlorophenyl)methyl]amino}-9-(methylethyl)purin-2-yl)amino]-3-methylbutanamide, (2-amino-2-methylpropyl)(6-{[(4-chlorophenyl)methyl]amino}-9-(methylethyl)purin-2-yl)amine, 3-(2-[bis(2-hydroxyethyl)amino]-6-{[4-chlorophenyl)methyl]amino}purin-9-yl)butan-2-one,
2-[(6-{[(4-chlorophenyl)methyl]amino}-9-(methylethyl)purin-2-yl)amino]-3-methylbutan-1-ol, 4-[({2-[(2-aminoethyl)amino]-9-(methylethyl)purin-6-yl}amino)methyl]benzenesulfonamide, 2-[(2-hydroxyethyl)(6-{[(4-methoxyphenyl)methyl]amino}-9-(methylethyl)purin-2-yl)amino]ethan-1-ol, 2-((2-hydroxyethyl){9-(methylethyl)-6-[(4-phenylphenyl)amino]purin-2-yl}amino)ethan-1-ol,

{2-[(2-amino-2-propyl)amino]-9-(methylethyl)purin-6-yl}[(4-hlorophenyl)methyl]amine, {2-[(2-aminoethyl)amino]-9-(methylethyl)purin-6-yl}[(4-chlorophenyl)methyl]amine, {2-[(2-aminopropyl)amino]-9-(methylethyl)purin-6-yl}[(4-chlorophenyl)methyl]amine and 2-[(2-aminoethyl)(6-{[(4-chlorophenyl)methyl]amino}-9-(methylethyl)purin-2-yl)amino]ethan-1-ol.

There are some limitations to the scope of R_1, R_1', R_2 and R_3. As mentioned above, when R_3 is 2-hydroxyethylamino and R_2 is methyl, R_1'-X cannot be amino, 3-methyl-2-butenylamino, benzylamino, or m-hydroxybenzyl-amino. When R_3 is 2-hydroxyethylamino and R_2 is isopropyl, R_1'-X cannot be benzylamino, m-hydroxybenzylamino, or 3-methylbutylamino. When R_3 is 2-hydroxyethylamino and R_2 is 2-hydroxyethyl, R_1'-X cannot be benzylamino. When R_3 is 2-propanol-2-methylamino or 2-dimethylaminoethylamino and R_2 is methyl, R_1'-X cannot be benzylamino.

The following are definitions for certain terms used herein.

"Halo" or "Halogen" - alone or in combination means all halogens, that is, chloro (Cl), fluoro (F), bromo (Br), iodo (I).

"Hydroxyl" refers to the group -OH.

"Thiol" or "mercapto" refers to the group -SH.

"Alkyl" - alone or in combination means an alkane-derived radical containing from 1 to 20, preferably 1 to 15, carbon atoms (unless specifically defined). It is a straight chain alkyl, branched alkyl or cycloalkyl. Preferably, straight or branched alkyl groups containing from 1-15, more preferably 1 to 8, even more preferably 1-6, yet more preferably 1-4 and most preferably 1-2, carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl and the like. The term "lower alkyl" is used herein to describe the straight chain alkyl groups

described immediately above. Preferably, cycloalkyl groups are monocyclic, bicyclic or tricyclic ring systems of 3-8, more preferably 3-6, ring members per ring, such as cyclopropyl, cyclopentyl, cyclohexyl, adamantyl and the like. Alkyl also includes a straight chain or branched alkyl group that contains or is interrupted by a cycloalkyl portion. The straight chain or branched alkyl group is attached at any available point to produce a stable compound. Examples of this include, but are not limited to, 4-(isopropyl)-cyclohexylethyl or 2-methyl-cyclopropylpentyl. A substituted alkyl is a straight chain alkyl, branched alkyl, or cycloalkyl group defined previously, independently substituted with 1 to 3 groups or substituents of halo, hydroxy, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyloxy, aryloxy, heteroaryloxy, amino optionally mono- or di-substituted with alkyl, aryl or heteroaryl groups, amidino, urea optionally substituted with alkyl, aryl, heteroaryl or heterocyclyl groups, aminosulfonyl optionally N-mono- or N,N-di-substituted with alkyl, aryl or heteroaryl groups, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, or the like.

"Alkenyl" - alone or in combination means a straight, branched, or cyclic hydrocarbon containing 2-20, preferably 2-17, more preferably 2-10, even more preferably 2-8, most preferably 2-4, carbon atoms and at least one, preferably 1-3, more preferably 1-2, most preferably one, carbon to carbon double bond. In the case of a cycloalkyl group, conjugation of more than one carbon to carbon double bond is not such as to confer aromaticity to the ring. Carbon to carbon double bonds may be either contained within a cycloalkyl portion, with the exception of cyclopropyl, or within a straight chain or branched portion. Examples of alkenyl groups include ethenyl, propenyl, isopropenyl, butenyl, cyclohexenyl, cyclohexenylalkyl and the like. A substituted alkenyl is the straight chain alkenyl, branched alkenyl or cycloalkenyl

group defined previously, independently substituted with 1 to 3 groups or substituents of halo, hydroxy, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyloxy, aryloxy, heteroaryloxy, amino optionally mono- or di-substituted with alkyl, aryl or heteroaryl groups, amidino, urea optionally substituted with alkyl, aryl, heteroaryl or heterocyclyl groups, aminosulfonyl optionally N-mono- or N,N-di-substituted with alkyl, aryl or heteroaryl groups, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, carboxy, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, or the like attached at any available point to produce a stable compound.

"Alkynyl" - alone or in combination means a straight or branched hydrocarbon containing 2-20, preferably 2-17, more preferably 2-10, even more preferably 2-8, most preferably 2-4, carbon atoms containing at least one, preferably one, carbon to carbon triple bond. Examples of alkynyl groups include ethynyl, propynyl, butynyl and the like. A substituted alkynyl refers to the straight chain alkynyl or branched alkenyl defined previously, independently substituted with 1 to 3 groups or substituents of halo, hydroxy, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyloxy, aryloxy, heteroaryloxy, amino optionally mono- or di-substituted with alkyl, aryl or heteroaryl groups, amidino, urea optionally substituted with alkyl, aryl, heteroaryl or heterocyclyl groups, aminosulfonyl optionally N-mono- or N,N-di-substituted with alkyl, aryl or heteroaryl groups, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, or the like attached at any available point to produce a stable compound.

"Alkyl alkenyl" refers to a group -R-CR'=CR''' R'''', where R is lower alkyl, or substituted lower alkyl, R', R''', R''''may independently be hydrogen, halogen, lower alkyl,

substituted lower alkyl, acyl, aryl, substituted aryl, hetaryl, or substituted hetaryl as defined below.

"Alkyl alkynyl" refers to a groups -RC≡CR' where R is lower alkyl or substituted lower alkyl, R' is hydrogen, lower alkyl, substituted lower alkyl, acyl, aryl, substituted aryl, hetaryl, or substituted hetaryl as defined below.

"Alkoxy" denotes the group -OR, where R is lower alkyl, substituted lower alkyl, acyl, aryl, substituted aryl, aralkyl, substituted aralkyl, heteroalkyl, heteroarylalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, or substituted cycloheteroalkyl as defined.

"Alkylthio" denotes the group -SR, $-S(O)_{n=1-2}-R$, where R is lower alkyl, substituted lower alkyl, aryl, substituted aryl, aralkyl or substituted aralkyl as defined herein.

"Acyl" denotes groups -C(O)R, where R is hydrogen, lower alkyl substituted lower alkyl, aryl, substituted aryl and the like as defined herein.

"Aryloxy" denotes groups -OAr, where Ar is an aryl, substituted aryl, heteroaryl, or substituted heteroaryl group as defined herein.

"Amino" denotes the group NRR', where R and R' may independently by hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl, hetaryl, or substituted hetaryl as defined herein or acyl.

"Amido" denotes the group -C(O)NRR', where R and R' may independently by hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl, hetaryl, substituted hetaryl as defined herein.

"Carboxyl" denotes the group -C(O)OR, where R is hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl, hetaryl, and substituted hetaryl as defined herein.

"Aryl" - alone or in combination means phenyl or naphthyl optionally carbocyclic fused with a cycloalkyl of preferably 5-7, more preferably 5-6, ring members and/or optionally substituted with 1 to 3 groups or substituents of halo, hydroxy, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyloxy, aryloxy, heteroaryloxy, amino optionally mono- or di-substituted with alkyl, aryl or heteroaryl groups, amidino, urea optionally substituted with alkyl, aryl, heteroaryl or heterocyclyl groups, aminosulfonyl optionally N-mono- or N,N-di-substituted with alkyl, aryl or heteroaryl groups, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, or the like.

"Substituted aryl" refers to aryl optionally substituted with one or more functional groups, *e.g.*, halogen, lower alkyl, lower alkoxy, alkylthio, acetylene, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Heterocycle" refers to a saturated, unsaturated, or aromatic carbocyclic group having a single ring (*e.g.*, morpholino, pyridyl or furyl) or multiple condensed rings (*e.g.*, naphthpyridyl, quinoxalyl, quinolinyl, indolizinyl or benzo[b]thienyl) and having at least one hetero atom, such as N, O or S, within the ring, which can optionally be unsubstituted or substituted with, *e.g.*, halogen, lower alkyl, lower alkoxy, alkylthio, acetylene, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Heteroaryl" - alone or in combination means a monocyclic aromatic ring structure containing 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing one or more, preferably 1-4, more preferably 1-3, even more preferably 1-2, heteroatoms

independently selected from the group O, S, and N, and optionally substituted with 1 to 3 groups or substituents of halo, hydroxy, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, acyloxy, aryloxy, heteroaryloxy, amino optionally mono- or di-substituted with alkyl, aryl or heteroaryl groups, amidino, urea optionally substituted with alkyl, aryl, heteroaryl or heterocyclyl groups, aminosulfonyl optionally N-mono- or N,N-di-substituted with alkyl, aryl or heteroaryl groups, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, or the like. Heteroaryl is also intended to include oxidized S or N, such as sulfinyl, sulfonyl and N-oxide of a tertiary ring nitrogen. A carbon or nitrogen atom is the point of attachment of the heteroaryl ring structure such that a stable aromatic ring is retained. Examples of heteroaryl groups are pyridinyl, pyridazinyl, pyrazinyl, quinazolinyl, purinyl, indolyl, quinolinyl, pyrimidinyl, pyrrolyl, oxazolyl, thiazolyl, thienyl, isoxazolyl, oxathiadiazolyl, isothiazolyl, tetrazolyl, imidazolyl, triazinyl, furanyl, benzofuryl, indolyl and the like. A substituted heteroaryl contains a substituent attached at an available carbon or nitrogen to produce a stable compound.

"Heterocyclyl" - alone or in combination means a non-aromatic cycloalkyl group having from 5 to 10 atoms in which from 1 to 3 carbon atoms in the ring are replaced by heteroatoms of O, S or N, and are optionally benzo fused or fused heteroaryl of 5-6 ring members and/or are optionally substituted as in the case of cycloalkyl. Heterocycyl is also intended to include oxidized S or N, such as sulfinyl, sulfonyl and N-oxide of a tertiary ring nitrogen. The point of attachment is at a carbon or nitrogen atom. Examples of heterocyclyl groups are tetrahydrofuranyl, dihydropyridinyl, piperidinyl, pyrrolidinyl, piperazinyl, dihydrobenzofuryl,

dihydroindolyl, and the like. A substituted hetercyclyl contains a substituent nitrogen attached at an available carbon or nitrogen to produce a stable compound.

"Substituted heteroaryl" refers to a heterocycle optionally mono or poly substituted with one or more functional groups, *e.g.*, halogen, lower alkyl, lower alkoxy, alkylthio, acetylene, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Aralkyl" refers to the group -R-Ar where Ar is an aryl group and R is lower alkyl or substituted lower alkyl group. Aryl groups can optionally be unsubstituted or substituted with, *e.g.*, halogen, lower alkyl, alkoxy, alkylthio, acetylene, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Heteroalkyl" refers to the group -R-Het where Het is a heterocycle group and R is a lower alkyl group. Heteroalkyl groups can optionally be unsubstituted or substituted with *e.g.*, halogen, lower alkyl, lower alkoxy, alkylthio, acetylene, amino, amido, carboxyl, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Heteroarylalkyl" refers to the group -R-HetAr where HetAr is an heteroaryl group and R lower alkyl or substituted lower alkyl. Heteroarylalkyl groups can optionally be unsubstituted or substituted with, *e.g.*, halogen, lower alkyl, substituted lower alkyl, alkoxy, alkylthio, acetylene, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Cycloalkyl" refers to a divalent cyclic or polycyclic alkyl group containing 3 to 15 carbon atoms.

"Substituted cycloalkyl" refers to a cycloalkyl group comprising one or more substituents with, *e.g.*, halogen, lower alkyl, substituted lower alkyl, alkoxy, alkylthio, acetylene, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Cycloheteroalkyl" refers to a cycloalkyl group wherein one or more of the ring carbon atoms is replaced with a heteroatom (*e.g.*, N, O, S or P).

"Substituted cycloheteroalkyl" refers to a cycloheteroalkyl group as herein defined which contains one or more substituents, such as halogen, lower alkyl, lower alkoxy, alkylthio, acetylene, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Alkyl cycloalkyl" denotes the group -R-cycloalkyl where cycloalkyl is a cycloalkyl group and R is a lower alkyl or substituted lower alkyl. Cycloalkyl groups can optionally be unsubstituted or substituted with *e.g.* halogen, lower alkyl, lower alkoxy, alkylthio, acetylene, amino, amido, carboxyl, hydroxyl, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Alkyl cycloheteroalkyl" denotes the group -R-cycloheteroalkyl where R is a lower alkyl or substituted lower alkyl. Cycloheteroalkyl groups can optionally be unsubstituted or substituted with *e.g.* halogen, lower alkyl, lower alkoxy, alkylthio, amino, amido, carboxyl, acetylene, hydroxyl, aryl, aryloxy, heterocycle, substituted heterocycle, hetaryl, substituted hetaryl, nitro, cyano, thiol, sulfamido and the like.

"Pharmacologically acceptable salt" - a salt prepared by conventional means, and are well known by those skilled in the art. The "pharmacologically acceptable salts" include basic salts of inorganic and organic acids, including but not limited to hydrochloric acid,

hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanesulfonic acid, malic acid, acetic acid, oxalic acid, tartaric acid, citric acid, lactic acid, fumaric acid, succinic acid, maleic acid, salicylic acid, benzoic acid, phenylacetic acid, mandelic acid and the like. When compounds of formula I-III include an acidic function such as a carboxy group, then suitable pharmaceutically acceptable cation pairs for the carboxy group are well known to those skilled in the art and include alkaline, alkaline earth, ammonium, quaternary ammonium cations and the like. For additional examples of the types of compounds that are "pharmacologically acceptable salts," *see* Berge et al, *J. Pharm. Sci.* 66, 1 (1977).

If the final 2,6,9-trisubstituted purine compound of this invention contains a basic group, then an acid addition salt of the composition may be prepared. Acid addition salts of the compounds of this invention are prepared in a standard manner in a suitable solvent from the parent compound and an excess of acid, such as, but not limited to, hydrochloric, hydrobromic, sulfuric, phosphoric, acetic, maleic, succinic, citric or methanesulfonic. The hydrochloric salt form is especially useful.

If the final 2,6,9-trisubstituted purine compound contains an acidic group, then cationic salts of the composition may be prepared. Typically the acidic parent compound is treated with an excess of an alkaline reagent, such as, but not limited to, hydroxide, carbonate or alkoxide, containing the appropriate cation such as but not limited to, Na^+, K^+, Ca^{+2} and NH_4^+. Certain of the compounds form inner salts or zwitterions which are also acceptable.

The compounds of this invention are useful in inhibiting cell proliferation in mammals including humans. The 2,6,9-trisubstituted purines are useful in for example in treating autoimmune diseases, e.g. rheumatoid arthritis, lupus, type I diabetes, multiple sclerosis, cancer, cardiovascular disease such as restenosis following balloon angioplasty and atherectomy, restensosis following vascular modifying surgical procedures, host vs graft disease, gout, polycystic kidney disease and other proliferative diseases whose pathogenesis involves abnormal cell proliferation. In particular, the compositions of this invention are useful in treating cancers including cancers including lymphoyd neoplasm, cancer of the colon, breast cancer, ovarian cancer, pancreatic cancer, and cancers derived of endotherical cells.

The method of treatment comprises the administration parenterally, and orally, of an effective quantity of the chosen compound of this invention, preferably dispersed in a pharmaceutical carrier. Therapeutically useful amounts of the composition of this invention will generally range from about 0.01 to about 100 mg/kg, but will be readily determined by one skilled in the art depending upon the route of administration, and the age and condition of the patient. Therapeutically useful amounts of the composition of this invention may be administered from one to ten times daily or more for acute or chronic disease. No unacceptable toxicological effects are expected when compounds of the invention are administered in accordance with the present invention.

The compounds of this invention are also useful as antiinflammatory and antifungal agents. As such, the compositions of this invention are useful for treating antiinflammatory and fungal infections in humans, animals, and fungal infections in plants.

Pharmaceutical compositions including the compounds of this invention, and/or

derivatives thereof, may be formulated as solutions or lyophilized powders for parenteral administration. Powders may be reconstituted by addition of a suitable diluent or other pharmaceutically acceptable carrier prior to use. If used in liquid form the compositions of this invention are preferably incorporated into a buffered, isotonic, aqueous solution. Examples of suitable diluents are normal isotonic saline solution, standard 5% dextrose in water and buffered sodium or ammonium acetate solution. Such liquid formulations are suitable for parenteral administration, but may also be used for oral administration.

It may be desirable to add excipients such as polyvinylpyrrolidinone, gelatin, hydroxycellulose, acaia, polyethylene glycol, mannitol, sodium chloride, sodium citrate or any other excipient known to one of skill in the art to pharmaceutical compositions including compounds of this invention. Alternatively, the pharmaceutical compounds may be encapsulated, tableted or prepared in an emulsion or syrup for oral administration. Pharmaceutically acceptable solid or liquid carriers may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Liquid carriers include, but are not limited to syrup, peanut oil, olive oil, glycerin, saline, alcohols and water. Solid carriers include, but are not limited to, starch, lactose, calcium sulfate, dihydrate, teffa alba, magnesium stearate or stearic acid, talc, pectin, acacia, agar or gelatin. The carrier may also include a sustained release material such as, but not limited to, glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies but, preferably, will be between about 20 mg to about 1 gram per dosage unit.

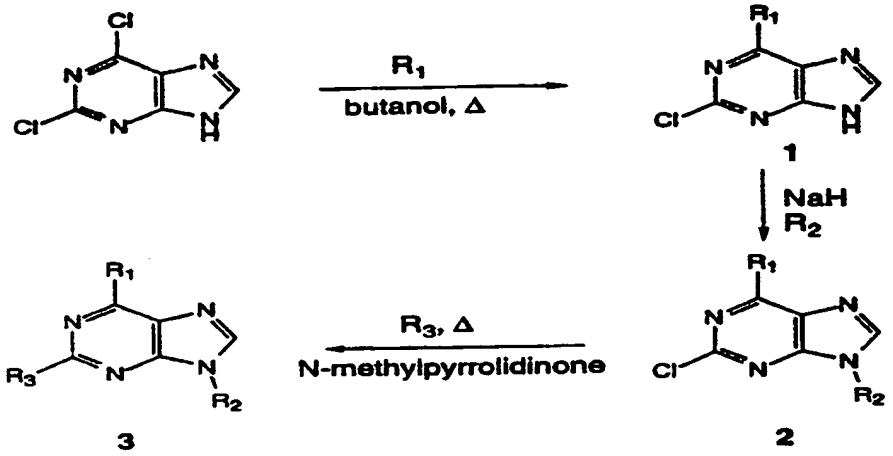
The pharmaceutical dosages are made using conventional techniques such as, but not limited to, milling, mixing, granulation, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used,

the preparation will be in the form of a syrup, elixir, emulsion or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered directly or filled into a soft gelatin capsule.

The Examples which follow serve to illustrate this invention. The Examples are intended to in no way limit the scope of this invention, but are provided to show how to make and use the compounds of this invention. In the Examples, all temperatures are in degrees Centigrade. RT indicates room temperature.

EXAMPLE 1

The compounds of this invention are prepared by conventional methods of organic chemistry. The reaction sequence outlined in the synthesis scheme below is a general method useful for the synthesis of compounds of this invention. 2,6-dichloropurine is dissolved in butanol and the appropriate R_1 amine is added. After heating for several hours, the reaction mixture is cooled, and the compound 1 is obtained. To compound 1, is added, sodium hydride followed by R_2, and compound 2 is isolated. To compound 2, R_3 is added in solution with N-methylpyrrolidinone. The mixture is heated for an appropriate period followed by purification leading to the desired compound.



The following compound was prepared according to the method above.

Preparation of 2-chloro-6-(4-methoxybenzylamino) purine (1).

The 2,6-dichloropurine (4.06 g, 21.5 mmol) was suspended in n-butanol (150 ml) and the 4-methoxybenzylamine was added (3.4 ml, 26 mmol). The solution turned clear and then cloudy a few minutes later. The solution was heated at 120°C for 2 hr and then cooled. The n-butanol was evaporated followed by suspension of the residue in water and diethyl ether

mixture. A solution of 2N NaOH (1.3ml, 26 mmol) was added and the solution stirred for 10 min before filtration. The filtered precipitate was washed with water and a small portion of ether and then dried under vacuum. The residual liquor was left overnight and more crystals were collected the next day and washed with diethyl ether.

Preparation of 2-chloro-6-(4-methoxybenzylamino)-9-isopropylpurine (2)

2-chloro-6-(4-methoxybenzylamino) purine was suspended in dry DMF (5 ml) and treated with sodium hydride, 60% dispersion (82 mg, 2.06 mmol). The suspension was stirred for 30 min over which time it became a clear yellow/green solution. 2-Iodopropane (0.280 mL, 1.7 eq.) was added over 5 min and the resultant solution stirred for 2 days. Water was added and the solution and extracted with ethyl acetate. The organic layer was evaporated to give the product isopropyl purine.

Preparation of 2-diethanolamino-6-(4-methoxybenzylamino)-9-isopropylpurine, (3).

The purine (1.65g, 4.98 mmol) was dissolved in DMSO (12 mL) and diethanolamine (4 mL) and then heated at 140°C for 2-3 days and then at 160°C for 1 day. The solution was cooled and water saturated butanol was added (100 mL). The solution was then washed with water (3 x 50 mL), before being evaporated to give a brown oil. The residue was chromatographed over silica gel eluting with ethyl acetate, followed by 3% methanol in ethyl acetate to give the product. ^{1}H-NMR(δ CDCl3): 7.29(br s 1H), 7.25(d, 2H), 6.94(br s. 1H), 6.83(d. 2H), 5.43(br s.<2H), 4.63(br s. 2H), 4.53(m 1H), 3.86(t. 4H), 3.76(m, 7H), 1.47(d 6H).

Table 1 identifies compounds of this invention that were prepared according to the synthesis method set forth in this Example.

TABLE 1
Compounds Prepared By The Method of Example 1

R_1X	R_2	R_3
(4-methoxyphenyl)methylamino	3-cyanopropyl	Cl
(4-methoxyphenyl)methylamino	3-chloropropyl	Cl
(4-methoxyphenyl)methylamino	benzyl	Cl
(4-methoxyphenyl)methylamino	(4-methylcarboxyphenyl)methyl	Cl
(4-methoxyphenyl)methylamino	2-(N-phtyhaloyl)ethyl	Cl
(4-methoxyphenyl)methylamino	isopropyl	Ethanolamine
(4-methoxyphenyl)methylamino	isopropyl	Diethanolamine
(4-methoxyphenyl)methylamino	3-methylbutyl	Cl
(4-methoxyphenyl)methylamino	2-methylbutyl	Cl
(4-methoxyphenyl)methylamino	cyclopentyl	Cl
(4-methoxyphenyl)methylamino	(3-nitrophenyl)methyl	Cl
(4-methoxyphenyl)methylamino	(4-nitrophenyl)methyl	Cl
(4-methoxyphenyl)methylamino	ethyl	Cl
(4-methoxyphenyl)methylamino	propyl	Cl
(4-methoxyphenyl)methylamino	(3-methylphenyl)methyl	Cl
(4-methoxyphenyl)methylamino	(4-methylphenyl)methyl	Cl
heptylamino	H	Cl
N-benzyl-N-hydroxylamino	H	Cl
propylamino	H	Cl
noradamantylamino	H	Cl
cyclobutylamino	H	Cl
3-methoxypropylamino	H	Cl
2-methoxyethylamino	H	Cl
cyclopentylamino	H	Cl
1-hydroxy-2-methyl-2-propylamino	H	Cl
(N-1-benzylpiperidinyl)-4-amino	H	Cl
heptylamino	Methyl	Cl

R_1X	R_2	R_3
N-benzyl-N-hydroxylamino	Methyl	Cl
propylamino	Methyl	Cl
noradamantylamino	Methyl	Cl
cyclobutylamino	Methyl	Cl
3-methoxypropylamino	Methyl	Cl
2-methoxyethylamino	Methyl	Cl
cyclopentylamino	Methyl	Cl
1-hydroxy-2-methyl-2-propylamino	Methyl	Cl
(N-1-benzylpiperidinyl)-4-amino	Methyl	Cl
(2,4-dimethoxyphenyl)methylamino	Methyl	Cl
(2-methoxyphenyl)methylamino	H	Cl
(2-pryidinyl)methylamino	H	Cl
(3,4-dimethoxyphenyl)ethylamino	H	Cl
(3-pyridinyl)methylamino	H	Cl
(4-pyridinyl)methylamino	H	Cl
6-hydroxy-1-hexylamino	H	Cl
phenethylamino	H	Cl
(2-benzothiazolyl)amino	H	Cl
(2,4-dimethoxyphenyl)methyalmino	H	Cl
(2-methoxyphenyl)methylamino	Methyl	Cl
(2-pyridinyl)methylamino	Methyl	Cl
(3,4-dimethoxyphenyl)ethylamino	Methyl	Cl

R_1-X	R_2	R_3
(4-methoxyphenyl)methylamino	Methyl	Cl
(3-pyridinyl)methylamino	isopropyl	2-aminoethylamino
(4-pyridinyl)methylamino	H	Cl
1-hydroxy-6-hexylamino	H	Cl
phenethylamino	H	Cl
(2-benzothiazolyl)amino	H	Cl
(4-methoxyphenyl)methylamino	H	Cl
3-phenyl-1-propylamino	isopropyl	3-hydroxypyrrolidino
(2-indanyl)amino	H	Cl
(4-methoxyphenyl)ethylamino	H	Cl
(4-nitrophenyl)methylamino	H	Cl
(2,6-difluorophenyl)methylamino	H	Cl
3-phenyl-1-propylamino	H	Cl
(2-indanyl)amino	Methyl	Cl
(4-methoxyphenyl)ethylamino	Methyl	Cl
(4-nitrophenyl)methylamino	Methyl	Cl
(2,6-difluorophenyl)methylamino	Methyl	Cl
cyclopropylmethylamino	Methyl	Cl
4-(1,2-methylenedioxyphenyl) methylamino	H	Cl
(4-aminosulfonylphenyl)methylamino	H	Cl
(cyclohexanol)-1-methylamino	H	Cl
(2-benzimidazoly)methylamino	H	Cl
cyclohexylmethylamino	H	Cl
(4-methoxyphenyl)methylamino	H	Cl

R_1-X	R_2	R_3
(4-methoxyphenyl)methylamino	isopropyl	(2-hydroxy-1-hydroxymethyl)ethylamino
cyclopropylmethylamino	isopropyl	3-amino-2-hydroxypropylamino
4-(1,2-methylene-dioxyphenyl)methylamino	Methyl	Cl
(4-aminosulfonyl-phenyl)methylamino	Methyl	Cl
(cyclohexanol)-1-methylamino	Methyl	Cl
(2-benzimidazolyl)methylamino	Methyl	Cl
cyclohexylmethylamino	Methyl	Cl
(3-pyridinyl)methylamino	Methyl	Cl
(4-pyridinyl)methylamino	2-methylpropyl	Cl
6-hydroxyhexylamino	cyclopentyl	Cl
phenethylamino	propyl	Cl
(2-benzothiazolyl)amino	ethyl	Cl
3-phenyl-1-propylamino	isopropyl	Cl
(2-indanyl)amino	2-methylpropyl	Cl
2-(4-methoxyphenyl)ethylamino	cyclopentyl	Cl
(4-nitrophenyl)methylamino	propyl	Cl
(2,6-difluorophenyl)methylamino	ethyl	Cl
(4-methoxyphenyl)methylamino	isopropyl	Cl
3-phenyl-1-propylamino	isopropyl	4-hydroxypiperidino
(2-indanyl)amino	H	Cl
2-(4-methoxyphenyl)ethylamino	H	Cl
(4-nitrophenyl)methylamimo	H	Cl
(2,6-difluorophenyl)methylamino	H	Cl

R_1-X	R_2	R_3
(4-methoxyphenyl)methylamino	H	Cl
(4-methoxyphenyl)methylamino	isopropyl	N-(2-cyanoethyl)-N-benzylamino
3-phyenyl-1-propylamino	isopropyl	1-(R,S)-hydroxymethyl-3-methylbutylamino
(2-indanyl)amino	isopropyl	Cl
2-(4-Methoxyphenyl)ethylamino	isopropyl	Cl
(4-nitrophenyl)methylamino	isopropyl	Cl
(2,6-difluorophenyl)methylamino	isopropyl	Cl
(4-methoxyphenyl)methylamino	isopropyl	Cl
(4-methoxyphenyl)methylamino	isopropyl	Piperidino
(4-methoxyphenyl)methylamino	isopropyl	3-hydroxypiperidino
3-phenyl-1-propylamino	isopropyl	1-(S)-hydroxymethyl-2-(4'-imidazolyl)ethylamino
(2-indanyl)amino	isopropyl	diethanolamino
(4-methyoxyphenyl)methylamino	isopropyl	diethanolamino
(4-methyoxyphenyl)methylamino	isopropyl	2-(S)-hydroxymethylpyrrolidino
(4-methyoxyphenyl)methylamino	isopropyl	diethanolamino
(4-methyoxyphenyl)methylamino	benzyl	morpholino
(4-methyoxyphenyl)methylamino	3-methylbutyl	diethanolamino
(4-methyoxyphenyl)methylamino	2-methylbutyl	diethanolamino
(4-methyoxyphenyl)methylamino	cyclopentyl	diethanolamino
(4-methyoxyphenyl)methylamino	(3-nitrophenyl)methylamino	diethanolamino
(4-methyoxyphenyl)methylamino	(4-nitrophenyl)methylamino	diethanolamino
(4-methyoxyphenyl)methylamino	ethyl	diethanolamino
(4-methyoxyphenyl)methylamino	propyl	diethanolamino
(4-methyoxyphenyl)methylamino	(3-methylphenyl)methylamino	diethanolamino
heptylamino	(4-methylphenyl)methylamino	diethanolamino

R_1-X	R_2	R_3
N-benzyl-N-hydroxyamino	Methyl	diethanolamino
propylamino	Methyl	diethanolamino
noradamantylamino	Methyl	diethanolamino
cyclobutylamino	Methyl	diethanolamino
3-methoxypropylamino	Methyl	diethanolamino
2-methoxyethylamino	Methyl	diethanolamino
cyclopentylamino	Methyl	diethanolamino
1-hydroxy-2-methyl-2-propylamino	Methyl	diethanolamino
4-(1-benzylpiperidinyl)amino	Methyl	diethanolamino
(4-methoxyphenyl)methylamino	Methyl	diethanolamino
(4-methoxyphenyl)methylamino	isopropyl	diethanolamino
(2,4-dimethoxy-phenyl) methylamino	isopropyl	3-hydroxypyrrolidino
(2-methoxyphenyl)methylamino	Methyl	2-(3'indolyl)ethylamino
(2-pyridinyl)methylamino	Methyl	diethanolamino
2-(3,4-dimethoxyphenyl)ethylamino	Methyl	diethanolamino
(3-pyridinyl)methylamino	Methyl	diethanolamino
(4-pyridinyl)methylamino	Methyl	diethanolamino
6-hydroxy-1-hexylamino	Methyl	diethanolamino
phenethylamino	Methyl	diethanolamino
(2-benzothiazolyl)amino	Methyl	diethanolamino
3-phenyl-1-propylamino	Methyl	diethanolamino
(2-indanyl)amino	Methyl	diethanolamino
2-(4-methoxyphenyl)ethylamino	Methyl	diethanolamino
(4-nitrophenyl)methylamino	Methyl	diethanolamino
(2,6-difluorophenyl)methylamino	Methyl	diethanolamino

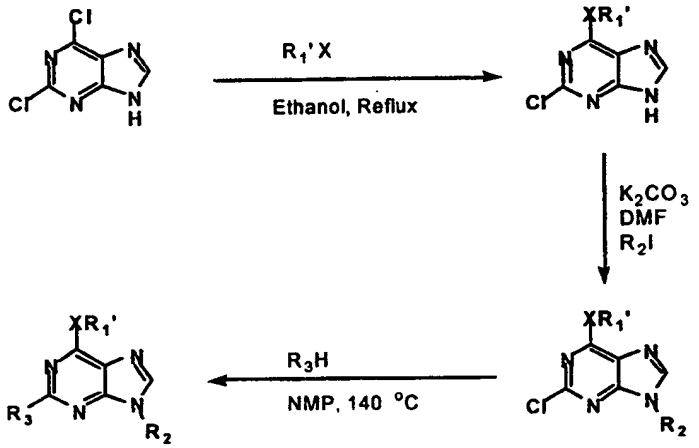
R_1-X	R_2	R_3
cyclopropylmethylamino	Methyl	diethanolamino
4-(1,2-methylenedioxy-phenyl)methylamino	Methyl	diethanolamino
(4-aminosulfonylphenyl)-methylamino	Methyl	diethanolamino
(cyclohexanol)-1-methylamino	Methyl	diethanolamino
(2-benzimidazolyl)methylamino	Methyl	diethanolamino
cyclohexylmethylamino	Methyl	diethanolamino
(3-pyridyl)methylamino	Methyl	diethanolamino
(4-pyridyl)methylamino	2-methylpropyl	diethanolamino
6-hydroxy-1-hexylamino	cyclopentyl	diethanolamino
2-phenethylamino	propyl	diethanolamino
(2-benzothiazolyl)amino	ethyl	diethanolamino
3-phenyl-1-propylamino	isopropyl	diethanolamino
(2-indanyl)amino	2-methylpropyl	diethanolamino
2-(4-methoxyphenyl)ethylamino	cyclopentyl	diethanolamino
(4-nitrophenyl)methylamino	propyl	diethanolamino
(2,6-difluorophenyl)methylamino	ethyl	diethanolamino
(4-methyoxyphenyl)methylamino	isopropyl	diethanolamino
(4-methyoxyphenyl)methylamino	isopropyl	1-hydroxymethylcyclopentylamino
(4-methyoxyphenyl)methylamino	isopropyl	2-(R,S)-hydroxymethylpiperidino
cyclopropylmethylamino	isopropyl	2,3-dihydroxy-1-propylamino
4-(1,2-methylenedioxyphenyl) methylamino	isopropyl	Cl
(4-aminosulfonylphenyl) methylamino	isopropyl	Cl
(cyclohexanol)-1-methylamino	isopropyl	Cl

R_1-X	R_2	R_3
(2-benzimidazolyl)amino	isopropyl	Cl
cyclohexylmethylamino	isopropyl	Cl
3-phenyl-1-propylamino	isopropyl	Cl
cyclopropylmethylamino	cyclopentyl	Cl
4-(1,2-methylenedioxyphenyl) methylamino	isopropyl	diethanolamino
(4-methoxyphenyl)methylamino	isopropyl	diethanolamino
(4-methoxyphenyl)methylamino	isopropyl	diisopropylamino
(4-methoxyphenyl)methylamino	isopropyl	(trans-2-hydroxycyclohexyl)amino
(4-methoxyphenyl)methylamino	isopropyl	2(R)-(1-hydroxy-3-phenyl)propylamino
(4-methoxyphenyl)methylamino	isopropyl	5-(S)-(2,2-dimethyl-4(S)-phenyldioxalanyl)amino
(4-methoxyphenyl)methylamino	isopropyl	3-(N-1-imidazolyl)propylamino
(4-methoxyphenyl)methylamino	isopropyl	4-hydroxyl-4-phenylpiperidino
(4-methoxyphenyl)methylamino	isopropyl	(2-benzylthio-1-hydroxymethyl)ethylamino
(4-methoxyphenyl)methylamino	isopropyl	N-methyl-N-(2-hydroxy-2-(3,4-dihydroxyphenyl)ethyl)amino
(4-methoxyphenyl)methylamino	isopropyl	diallylamino
(4-methoxyphenyl)methylamino	isopropyl	Piperazino
(4-methoxyphenyl)methylamino	isopropyl	(+/-)N-methyl-N-(2-hydroxy-2-phenylethyl)amino
(4-methoxyphenyl)methylamino	isopropyl	(S)-(+)-2-(anilinomethyl)pyrrolidino
(4-methoxyphenyl)methylamino	isopropyl	(+/-)N-(2-propenyl)-N-2-(4-hydroxy-2-methylpentyl)amino
(4-methoxyphenyl)methylamino	isopropyl	N-(2-hydroxyethyl)-N-(3-hydroxypropyl)amino

R_1'-X	R2	R3
(4-methoxyphenyl)methylamino	isopropyl	Di-N-1-(2-hydroxy-2-methylpentyl)amino
(4-methoxyphenyl)methylamino	isopropyl	Di-N-2-(3-hydroxybutyl)amino

Example 2

This example describes a method for preparing compounds of this invention according to the following general synthesis scheme:



Preparation of {2-chloropurin-6-yl}[(4-chlorophenyl)methyl]amine:

To a suspension of 15 g (0.0794 mol) of 2,6-dichloropurine in 250 mL of absolute ethanol was added 12.7 mL (0.0873 mol) of triethylamine and 10.62 mL (0.0873 mol) of 4-chlorobenzylamine. The mixture was refluxed at 80 °C for 16h (the formation of creamy white precipitate was observed). The reaction mixture was cooled and the precipitated product was removed by filtration. The precipitate was washed with ethanol (350 mL) and dried in high vacuum for 24h. Product was characterized by ^{1}H-NMR.

Preparation of {2-chloro-9-(methylethyl)purin-6-yl}[4-chlorophenyl)methyl]amine:

To a solution of 6 g (0.020 mol) of 2-chloro-6-(4-chlorophenyl)methylaminopurine in 41 mL of anhydrous DMF was added 5.64 g (0.041mol) anhydrous. potassium carbonate and 3.41 mL,(0.035 mol of 2-iodopropane) and stirred at room temperature for 16h. To the mixture 500 mL of water was added and stirred for 1h. The precipitate was filtered, washed with

water (350 mL), and dried in vacuum oven at 50 °C for 16h. The product was obtained as an off white solid and characterized by ^{1}H-NMR.

Preparation of {2-[(2-aminoethyl)amino]-9-(methylethyl)purin-6-yl}[(4-chlorophenyl)methyl]amine:

To a solution of 3.36 g (0.01 mol) of {2-chloro-9-(methylethyl)purin-6-yl}[4-chlorophenyl)methyl]amine in 13 mL of anhy. 1-methyl-2-pyrrolidinone was added 4.68 mL (0.70 mol) of 2-aminoethylamine and the mixture was heated at 140 °C for 24h. The compound was subjected to variable gradient chromatography on silica gel with dichloromethane/methanol mixtures and yielded 1-methyl-2-pyrrolidinone. The mixture was dissolved in dichloromethane and extracted with water (520 mL). The organic layer was dried over anhydrous. Sodium sulfate and evaporated to an off white solid. The product was characterized by ^{1}H-NMR and purity checked by RP-HPLC (YMC C-18 column; 50X4.4 mm; S-5 120 A° 0.1% TFA-water/ 0.1% TFA-acetonitrile).

Table 2, below identifies compounds of this invention that were prepared according to the general synthesis method set forth in this Example. In Table 2, MS = Mass Spectrum and MH+ = mass of parent molecular ion plus one hydrogen atom.

TABLE 2
COMPOUNDS PREPARED BY METHOD OF EXAMPLE 2

R_1X	R_2	R_3	MS(MH+)
(4-Methylphenyl)methylamino	Isopropyl	2-Aminoethylamino	340
(2,4-Dichlorophenyl)methylamino	Isopropyl	Diethanolamino	439
(2,4-Dichlorophenyl)methylamino	Isopropyl	2-Aminoethylamino	394
(3-Methylphenyl)methylamino	Isopropyl	Diethanolamino	385
(3-Methylphenyl)methylamino	Isopropyl	2-Aminoethylamino	340
(3-Methylphenyl)methylamino	Isopropyl	2-(N2-Dimethylamino)-N1-benzylethylamino	458
(4-Trifluoromethylphenyl)methylamino	Isopropyl	2-Aminoethylamino	394
(4-Trifluoromethylphenyl)methylamino	Isopropyl	1-Hydroxymethyl-2-methylpropylamino	437
(3,5-Bis-trifluoromethylphenyl)methylamino	Isopropyl	Diethanolamino	507
(3,5-Bis-trifluoromethylphenyl)methylamino	Isopropyl	2-Aminoethylamino	462

R_1X	R_2	R_3	MS(MH+)
(3,5-Bis-trifluoromethylphenyl)methylamino	Isopropyl	1-Hydroxymethyl-2-methylpropylamino	505
(3-Chlorophenyl)methylamino	Isopropyl	1-Hydroxymethylethylamino	375
(2-Trifluoromethyl-phenyl)methylamino	Isopropyl	1-Hydroxymethylethylamino	409
(4-Chloro-3-trifluoromethyl-phenyl)methylamino	Isopropyl	1-Hydroxymethylethylamino	443
(3-Chlorophenyl)methylamino	Isopropyl	2-Hydroxyethylamino	361
(2-Trifluromethyl-phenyl)methylamino	Isopropyl	2-Hydroxyethylamino	395
(4-Chloro-3-trifluoromethyl-phenyl)methylamino	Isopropyl	2-Hydroxyethylamino	429
(3-Chlorophenyl)methylamino	Isopropyl	(1R,2S)-2-Hydroxy-1-methyl-2-phenylethylamino	451
(2-Chlorophenyl)methylamino	Isopropyl	Diethanolamino	450
(2,5-Difluorophenyl)methylamino	Isopropyl	Diethanolamino	407
(1-Naphthyl)methylamino	Isopropyl	Diethanolamino	421
(2-Chlorophenyl)methylamino	Isopropyl	2-Aminoethylamino	360
(2,5-Difluorophenyl)methylamino	Isopropyl	2-Aminoethylamino	362
(1-Naphthyl)methylamino	Isopropyl	2-Aminoethylamino	376
(2-Chlorophenyl)methylamino	Isopropyl	1-Hydroxymethyl-2-methylethylamino	403
(2,5-Difluorophenyl)methylamino	Isopropyl	1-Hydroxymethyl-2-methylethylamino	405
(1-Naphthyl)methylamino	Isopropyl	1-Hydroxymethyl-2-methylethylamino	419
(3-Methylphenyl)methylamino	Isopropyl	2-Aminopropylamino	354
(2-Chlorophenyl)methylamino	Isopropyl	2-Aminopropylamino	374
(3-Chlorophenyl)methylamino	Isopropyl	2-Aminopropylamino	374
(2,5-Difluorophenyl)methylamino	Isopropyl	2-Aminopropylamino	376
(1-Naphthyl)methylamino	Isopropyl	2-Aminopropylamino	390
(2-Chloro-5-trifluoromethylphenyl)methylamino	Isopropyl	Diethanolamino	473
(3-Chlorophenyl)methylamino	Isopropyl	1-Hydroxymethyl-2-methylpropylamino	403
(2-Trifluoromethylphenyl)methylamino	Isopropyl	1-Hydroxymethyl-2-methylpropylamino	437
(3-Methylphenyl)methylamino	Isopropyl	2-(2-Hydroxyethylamino)-ethylamino	384
(2-Chlorophenyl)methylamino	Isopropyl	2-(2-Hydroxyethylamino)-ethylamino	404
(3-Chlorophenyl)methylamino	Isopropyl	2-(2-Hydroxyethylamino)-ethylamino	404
(2,5-Difluorophenyl)methylamino	Isopropyl	2-(2-Hydroxyethylamino)-ethylamino	406
(1-Naphthyl)methylamino	Isopropyl	2-(2-Hydroxyethylamino)-ethylamino	420
(3,5-Bistrifluoromethyl-phenyl)methylamino	Isopropyl	2-(2-Hydroxyethylamino)-ethylamino	506
(4-Isopropylphenyl)methylamino	Isopropyl	2-(2-Hydroxyethylamino)-ethylamino	412
(2-Trifluoromethylphenyl)methylamino	Isopropyl	2-(2-Hydroxyethylamino)-ethylamino	438
(4-Methylphenyl)methylamino	Isopropyl	2-(2-Hydroxyethylamino)-ethylamino	384

R_1X	R_2	R_3	MS(MH+)
(4-Chloro-3-trifluoromethylphenyl)methylamino	Isopropyl	2-(2-Hydroxyethylamino)-ethylamino	472
(2-Chloro-5-trifluoromethylphenyl)methylamino	Isopropyl	2-(2-Hydroxyethylamino)-ethylamino	472
(3,5-Dichlorophenyl)methylamino	Isopropyl	2-(2-Hydroxyethylamino)-ethylamino	438
(1R)-(4-Methylphenyl)ethylamino	Isopropyl	2-(2-Hydroxyethylamino)-ethylamino	398
(1R)-(2-Naphthyl)ethylamino	Isopropyl	2-(2-Hydroxyethylamino)-ethylamino	434
(2,4-Dichloro-6-methylphenyl)methylamino	Isopropyl	2-(2-Hydroxyethylamino)-ethylamino	452
(4-Trifluoromethylphenyl)methylamino	Isopropyl	2-(2-Hydroxyethylamino)-ethylamino	438
(3-Methylphenyl)methylamino	Isopropyl	(2S)-pyrrolomethylamino	380
(2-Chlorophenyl)methylamino	Isopropyl	(2S)-pyrrolomethylamino	400
(3-Chlorophenyl)methylamino	Isopropyl	(2S)-pyrrolomethylamino	400
(2,5-Difluorophenyl)methylamino	Isopropyl	(2S)-pyrrolomethylamino	402
(1-Naphthyl)methylamino	Isopropyl	(2S)-pyrrolomethylamino	416
(3,5-Bistrifluoromethyl-phenyl)methylamino	Isopropyl	(2S)-pyrrolomethylamino	502
(4-Isopropylphenyl)methylamino	Isopropyl	(2S)-pyrrolomethylamino	408
(2-Trifluoromethylphenyl)methylamino	Isopropyl	(2S)-pyrrolomethylamino	434
(4-Methylphenyl)methylamino	Isopropyl	(2S)-pyrrolomethylamino	380
(4-Chloro-3-trifluoromethylphenyl)methylamino	Isopropyl	(2S)-pyrrolomethylamino	468
(2-Chloro-5-trifluoromethylphenyl)methylamino	Isopropyl	(2S)-pyrrolomethylamino	468
(3,5-Dichlorophenyl)methylamino	Isopropyl	(2S)-pyrrolomethylamino	434
(1R)-(4-Methylphenyl)ethylamino	Isopropyl	(2S)-pyrrolomethylamino	394
(1R)-(2-Naphthyl)ethylamino	Isopropyl	(2S)-pyrrolomethylamino	430
(2,4-Dichloro-6-methylphenyl)methylamino	Isopropyl	(2S)-pyrrolomethylamino	448
(4-Trifluoromethylphenyl)methylamino	Isopropyl	(2S)-pyrrolomethylamino	434
(3-Methylphenyl)methylamino	Isopropyl	2-Hydroxy-1-(S)-methylethylamino	355
(2-Chlorophenyl)methylamino	Isopropyl	2-Hydroxy-1-(S)-methylethylamino	375
(2,5-Difluorophenyl)methylamino	Isopropyl	2-Hydroxy-1-(S)-methylethylamino	377
(1-Naphthyl)methylamino	Isopropyl	2-Hydroxy-1-(S)-methylethylamino	391
(3,5-Bistrifluoromethyl-phenyl)methylamino	Isopropyl	2-Hydroxy-1-(S)-methylethylamino	477
(4-Isopropylphenyl)methylamino	Isopropyl	2-Hydroxy-1-(S)-methylethylamino	383
(4-Methylphenyl)methylamino	Isopropyl	2-Hydroxy-1-(S)-methylethylamino	355
(2-Chloro-5-trifluoromethylphenyl)methylamino	Isopropyl	2-Hydroxy-1-(S)-methylethylamino	443
(5-Fluoro-2-trifluoromethylphenyl)methylamino	Isopropyl	2-Hydroxy-1-(S)-methylethylamino	427
(3,5-Dichlorophenyl)methylamino	Isopropyl	2-Hydroxy-1-(S)-methylethylamino	409

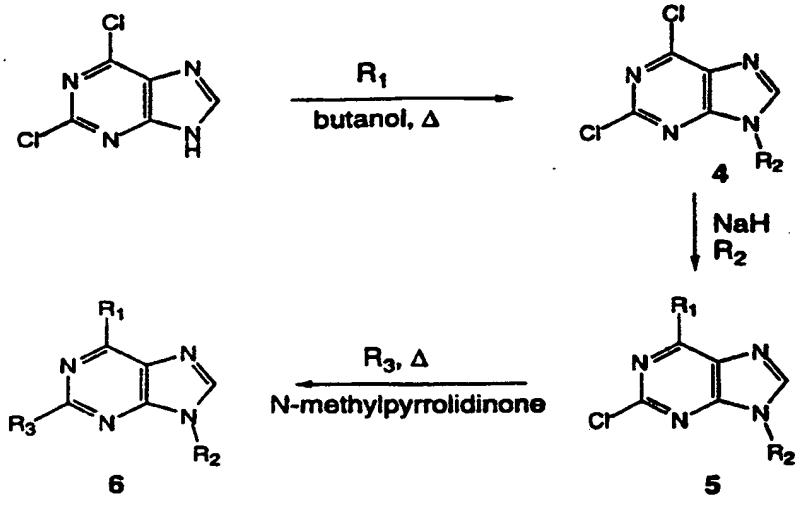
R_1X	R_2	R_3	MS(MH+)
[R]-1-(4-Methylphenyl)ethylamino	Isopropyl	2-Hydroxy-1-(S)-methylethylamino	369
[R]-1-(2-Naphthyl)ethylamino	Isopropyl	2-Hydroxy-1-(S)-methylethylamino	405
(2,4-Dichlorophenyl)methylamino	Isopropyl	2-Hydroxy-1-(S)-methylethylamino	409
(2,4-Dichloro-6-methylphenyl)methylamino	Isopropyl	2-Hydroxy-1-(S)-methylethylamino	423
(4-Trifluoromethylphenyl)methylamino	Isopropyl	2-Hydroxy-1-(S)-methylethylamino	409
(3-Methylphenyl)methylamino	Isopropyl	2-Hydroxyethylamino	341
(2-Chlorophenyl)methylamino	Isopropyl	2-Hydroxyethylamino	361
(2,5-Difluorophenyl)methylamino	Isopropyl	2-Hydroxyethylamino	363
(1-Naphthyl)methylamino	Isopropyl	2-Hydroxyethylamino	377
(3,5-Bistrifluoromethyl-phenyl)methylamino	Isopropyl	2-Hydroxyethylamino	463
(4-Isopropylphenyl)methylamino	Isopropyl	2-Hydroxyethylamino	369
(4-Methylphenyl)methylamino	Isopropyl	2-Hydroxyethylamino	341
(2-Chloro-5-trifluoromethylphenyl)methylamino	Isopropyl	2-Hydroxyethylamino	429
(5-Fluoro-2-trifluoromethylphenyl)methylamino	Isopropyl	2-Hydroxyethylamino	413
(3,5-Dichlorophenyl)methylamino	Isopropyl	2-Hydroxyethylamino	395
(1R)-(4-Methylphenyl)ethylamino	Isopropyl	2-Hydroxyethylamino	355
(1R)-(2-Naphthyl)ethylamino	Isopropyl	2-Hydroxyethylamino	391
(2,4-Dichlorophenyl)methylamino	Isopropyl	2-Hydroxyethylamino	395
(2,4-Dichloro-6-methylphenyl)methylamino	Isopropyl	2-Hydroxyethylamino	409
(4-Trifluoromethylphenyl)methylamino	Isopropyl	2-Hydroxyethylamino	395
(3-Methylphenyl)methylamino	Isopropyl	1-Hydroxymethylpropylamino	369
(2-Chlorophenyl)methylamino	Isopropyl	1-Hydroxymethylpropylamino	389
(3-Chlorophenyl)methylamino	Isopropyl	1-Hydroxymethylpropylamino	389
(2,5-Difluorophenyl)methylamino	Isopropyl	1-Hydroxymethylpropylamino	391
(1-Naphthyl)methylamino	Isopropyl	1-Hydroxymethylpropylamino	405
(3,5-Bistrifluoromethyl-phenyl)methylamino	Isopropyl	1-Hydroxymethylpropylamino	491
(4-Isopropylphenyl)methylamino	Isopropyl	1-Hydroxymethylpropylamino	397
(2-Trifluoromethylphenyl)methylamino	Isopropyl	1-Hydroxymethylpropylamino	423
(4-Methylphenyl)methylamino	Isopropyl	1-Hydroxymethylpropylamino	369
(4-Chloro-3-trifluoromethylphenyl)methylamino	Isopropyl	1-Hydroxymethylpropylamino	457
(2-Chloro-5-trifluoromethylphenyl)methylamino	Isopropyl	1-Hydroxymethylpropylamino	457
(5-Fluoro-2-trifluoromethylphenyl)methylamino		1-Hydroxymethylpropylamino	441

R_1X	R_2	R_3	MS(MH+)
(3,5-Dichlorophenyl)methylamino	Isopropyl	1-Hydroxymethylpropylamino	423
(1R)-(4-Methylphenyl)ethylamino	Isopropyl	1-Hydroxymethylpropylamino	383
(1R)-(2-Naphthyl)ethylamino	Isopropyl	1-Hydroxymethylpropylamino	419
(2,4-Dichlorophenyl)methylamino	Isopropyl	1-Hydroxymethylpropylamino	423
(2,4-Dichloro-6-methylphenyl)methylamino	Isopropyl	1-Hydroxymethylpropylamino	437
(4-Trifluoromethylphenyl)methylamino	Isopropyl	1-Hydroxymethylpropylamino	423
(3,5-Dichlorophenyl)methylamino	Isopropyl	2-(2-Hydroxyethylamino)-ethylamino	438
(3,5-Dichlorophenyl)methylamino	Isopropyl	(2S)-pyrrolomethylamino	434
(4-Chlorophenyl)methylamino	Isopropyl	2-Aminocyclohexylamino	414
(4-Chlorophenyl)methylamino	Isopropyl	3-Aminocyclohexylamino	414
(3-Fluoro-6-trifluoromethyl-phenyl)methylamino	Isopropyl	Diethanolamino	457
(2-Chloro-5-trifluoromethyl-pehnyl)methylamino	Isopropyl	2-Aminoethylamino	428
(3,5-Bis-trifluoromethyl-phenyl)methylamino	Isopropyl	2-Aminopropylamino	476
(2-Trifluoromethyl-phenyl)methylamino	Isopropyl	2-Aminopropylamino	408
(4-methylphenyl)methylamino	Isopropyl	2-Aminopropylamino	354
(4-Chloro-3-trifluoromethyl-phenyl)methylamino	Isopropyl	2-Aminopropylamino	442
(2-Chloro-5-trifluoromethyl-phenyl)methylamino	Isopropyl	2-Aminopropylamino	442
[R]-1-(4-methylphenyl)ethylamino	Isopropyl	2-aminoethylamino	354
[R]-1-(2-Naphthyl)ethylamino	Isopropyl	2-Aminoethylamino	390
(2-Chloro-5-trifluoromethyl-phenyl)methylamino	Isopropyl	1-Hydroxymethyl-2-methylpropylamino	471
(3-fluoro-6-trifluoromethyl-phenyl)methylamino	Isopropyl	1-Hydroxymethyl-2-methylpropylamino	455
[R]-1-(4-methylphenyl)ethylamino	Isopropyl	2-Aminopropylamino	368
[R]-1-(2-Naphthyl)ethylamino	Isopropyl	2-Aminopropylamino	404
(4-Trifluoromethyl-phenyl)methylamino	Isopropyl	2-Aminopropylamino	408
(3-Methylphenyl)methylamino	Isopropyl	2-Amino-2-methylpropylamino	368
(2-Chlorophenyl)methylamino	Isopropyl	2-Amino-2-methylpropylamino	388
(3-Chlorophenyl)methylamino	Isopropyl	2-Amino-2-methylpropylamino	388
(2,5-Difluorophenyl)methylamino	Isopropyl	2-Amino-2-methylpropylamino	390
(1-Naphthyl)methylamino	Isopropyl	2-Amino-2-methylpropylamino	404
(3,5-Bis-trifluoromethyl-phenyl)methylamino	Isopropyl	2-Amino-2-methylpropylamino	490
(2-Trifluoromethyl-phenyl)methylamino	Isopropyl	2-Amino-2-methylpropylamino	422
(4-Methylphenyl)methylamino	Isopropyl	2-Amino-2-methylpropylamino	368

R_1X	R_2	R_3	MS(MH+)
(4-Chloro-3-trifluoromethyl-phenyl)methylamino	Isopropyl	2-Amino-2-methylpropylamino	456
(2-Chloro-5-trifluoromethyl-phenyl)methylamino	Isopropyl	2-Amino-2-methylpropylamino	456
(3-Fluoro-6-trifluoromethyl-phenyl)methylamino	Isopropyl	2-Amino-2-methylpropylamino	440
[R]-1-(4-Methylphenyl)ethylamino	Isopropyl	2-Amino-2-methylpropylamino	382
[R]-1-(2-Naphthyl)ethylamino	Isopropyl	2-Amino-2-methylpropylamino	418
(4-Trifluoromethyl-phenyl)methylamino	Isopropyl	2-Amino-2-methylpropylamino	422

EXAMPLE 3

This Example describes a method for preparing compounds of this invention. The synthesis method disclosed in this Example is only slightly modified from that disclosed in Example 1.



The following compound was prepared according to the method above.

Preparation of 2,6-dichloro-9-isopropylpurine (4).

To a solution of 0.67g of 2,6-dichloropurine in 5mL of dry DMF at room temperature

was added 0. 16gms (l. 1 eq.) of 50% sodium hydride/oil powder. Upon cessation of hydrogen evolution, a large excess (2 mL) of isopropyl iodide was added to the anionic solution. This reaction solution was stirred for three days at ambient temperature. The reaction was quenched with 30 mL of water and extracted with ethyl acetate (350 mL). The organic extracts were combined and back washed with 350 mL of water followed by 20 mL of brine. The ethyl acetate solution was dried over anhydrous magnesium sulfate and evaporated. The compound was subjected to variable gradient flash chromatography on silica gel with hexane/ethyl acetate mixtures and yielded the N-9 product and the N-7 isomer.

Preparation of 2-chloro-6-anilino-9-isopropylpurine (5).

2,6-dichloro-9-isopropylpurine (0.019 g, 0.081 mmol) was dissolved in butanol (0.5 ml) and aniline (0.044 ml, 0.244 mmol) was added. The reaction mixture was heated to 120°C for 10 hr, cooled, diluted with EtOAc and washed 3 times with water. The mixture was dried over $MgSO_4$ and concentrated to an off white solid.

Preparation of 2-diethanolamino-6-(4-phenylanilino)-9-isopropylpurine (6).

A solution of 67mgs of 2,6-dichloro-N-9-isopropylpurine and 100mgs of 4-phenylaniline in 1 mL of n-octanol was heated to 80°C for 24 hours. The n-octanol was removed in vacuo and then replaced with 1 mL of 40% diethanolamine in DMSO. The solution was heated at 130°C for 48 hours. The reaction was cooled to ambient temperature then diluted with 10 mL of water and subsequently extracted with ethyl acetate (3X30 mL). The organic extracts were combined and back washed with 3X20 mL of water followed by 10 mL of brine. The ethyl acetate solution was dried over anhydrous magnesium sulfate and filtered and the solvent was evaporated. The 65mgs of crude product was

crystallized from THF-ether solution.

Table 3 below identifies compounds of this invention that were prepared according to the general synthesis method set forth in this Example.

TABLE 3
Compounds Prepared By The Method Of Example 3

R_1X	R_2	R_3
(8-quinolinyl)amino	Isopropyl	Cl
(6-quinolinyl)amino	Isopropyl	Cl
(3-quinolinyl)amino	Isopropyl	Cl
anilino	Isopropyl	Cl
3,5-dinitroanilino	Isopropyl	Cl
4-butylanilino	Isopropyl	Cl
(8-quinolinyl)amino	Isopropyl	Diethanolamino
(6-quinolinyl)amino	Isopropyl	Diethanolamino
(3-quinolinyl)amino	Isopropyl	Diethanolamino
anilino	Isopropyl	Diethanolamino
3,5-dinitroanilino	Isopropyl	Diethanolamino
4-butylanilino	Isopropyl	Diethanolamino
(6-ethoxy-2-benzothiazolyl)amino	Isopropyl	Cl
4-morpholino-2-methylamino	Isopropyl	Cl
(4-aminosulfonyl-phenyl)methylamino	Isopropyl	Cl
4-bromoanilino	Isopropyl	diethanolamino
3,4-dichloroanilino	Isopropyl	diethanolamino
2-(2-(1-methyl)pyrrolidinyl)ethylamino	Isopropyl	diethanolamino
3-bromoanilino	Isopropyl	Cl
4-methoxyanilino	Isopropyl	diethanolamino
4-iodoanilino	Isopropyl	Cl
3-iodoanilino	Isopropyl	Cl
3-methoxyanilino	Isopropyl	Cl
2-(1-piperidinyl)ethylamino	Isopropyl	diethanolamino
2-(1-pyrrolidinyl)ethylamino	Isopropyl	diethanolamino
(1-indanyl)amino	Isopropyl	diethanolamino
2-(6-ethoxybenzothiazolyl)amino	Isopropyl	diethanolamino
4-morpholino-2-methylamino	Isopropyl	diethanolamino
(4-aminosulfonyl-phenyl)methylamino	Isopropyl	diethanolamino
4-bromoanilino	Isopropyl	diethanolamino
3,4-dichloroanilino	Isopropyl	diethanolamino
2-(2-(1-methyl)pyrrolidinyl)ethylamino	Isopropyl	diethanolamino
3-bromoanilino	Isopropyl	diethanolamino
4-methyoxyanilino	Isopropyl	diethanolamino
4-iodoanilino	Isopropyl	diethanolamino
3-iodoanilino	Isopropyl	diethanolamino
3-methoxyanilino	Isopropyl	diethanolamino
2-(1-piperidinyl)ethylamino	Isopropyl	diethanolamino
2-(1-pyrrolidinyl)ethylamino	Isopropyl	diethanolamino
(1-indanyl)amino	Isopropyl	diethanolamino
3-iodonilino	Isopropyl	diethanolamino

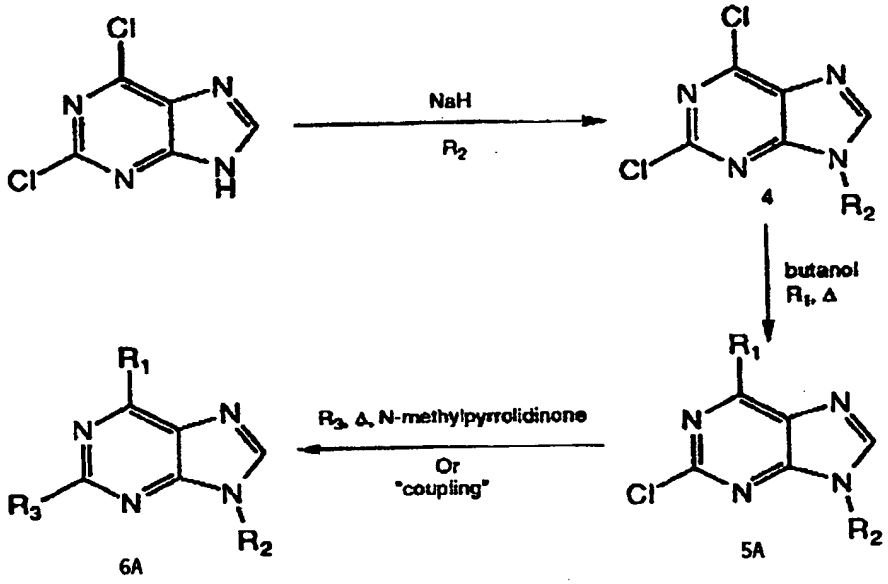
R_1X	R_2	R_3
3-phenoxyanilino	Isopropyl	diethanolamino
4-iodoanilino	Isopropyl	diethanolamino
4-phenoxyanilino	Isopropyl	diethanolamino
3-phenoxyanilino	Isopropyl	diethanolamino
2-fluorenylamino	Isopropyl	diethanolamino
1-fluorenylamino	Isopropyl	diethanolamino
2-anthracenylamino	Isopropyl	diethanolamino
1-anthracenylamino	Isopropyl	diethanolamino
2-(6-ethoxybenzothiazolyl)amino	Isopropyl	diethanolamino
(1-indanyl)amino	Isopropyl	diethanolamino
2-(6-ethoxybenzothiazolyl)amino	Isopropyl	diethanolamino
4-morpholino-2-methylamino	Isopropyl	diethanolamino
(4-aminosulfonyl-phenyl)methylamino	Isopropyl	diethanolamino
4-bromoanilino	Isopropyl	diethanolamino
3,4-dichloroanilino	Isopropyl	diethanolamino
2-(2-(1-methyl)pyrrolidinyl)ethylamino	Isopropyl	diethanolamino
3-bromoanilino	Isopropyl	diethanolamino
4-methoxyanilino	Isopropyl	diethanolamino
4-iodoanilino	Isopropyl	diethanolamino
3-iodoanilino	Isopropyl	diethanolamino
3-methoxyanilino	Isopropyl	diethanolamino
2-(1-piperidinyl)ethylamino	Isopropyl	diethanolamino
2-(1-pyrrolidinyl)ethylamino	Isopropyl	diethanolamino
(1-indanyl)amino	Isopropyl	diethanolamino
3-iodoanilino	Isopropyl	diethanolamino
3-pheoxyanilino	Isopropyl	diethanolamino
4-iodonilino	Isopropyl	diethanolamino
4-phenoxyanilino	Isopropyl	diethanolamino
3-phenoxyanilino	Isopropyl	diethanolamino
2-fluorenylamino	Isopropyl	diethanolamino
1-fluorenylamino	Isopropyl	diethanolamino
2-anthracenylamino	Isopropyl	diethanolamino
1-anthracenylamino	Isopropyl	diethanolamino
2-(6-ethoxybenzothiazolyl)amino	Isopropyl	diethanolamino
(2-biphenyl)methylamino	Isopropyl	diethanolamino
(4-biphenyl)methylamino	Isopropyl	diethanolamino
2-naphthylmethylamino	Isopropyl	diethanolamino
1-naphthylmethylamino	Isopropyl	diethanolamino
(4-Chlorophenyl)methylamino	Isopropyl	Diethanolamino
(4-Fluorophenyl)methylamino	Isopropyl	Diethanolamino
(4-Methoxyphenyl)methylamino	Isopropyl	5-Aminopentylamino
(4-Trifluoromethylphenyl)methylamino	Isobutyl	Diethanolamino
(4-Trifluoromethylphenyl)methylamino	Isopropyl	Diethanolamino
(4-Chlorophenyl)methylamino	Isopropyl	(S)-2-Amino-3-phenylpropylamino
(4-Fluorophenyl)methylamino	Isopropyl	2-Aminoethylamino
(4-Fluorophenyl)methylamino	Isopropyl	(D)-1-Hydroxymethyl-2-methyl-propylamino
(4-Fluorophenyl)methylamino	Isopropyl	(L)-1-Hydroxymethyl-2-methyl-propylamino
(4-Chlorophenyl)methylamino	Isopropyl	(D)-1-Hydroxymethyl-2-methyl-propylamino

R_1X	R_2	R_3
(4-Chlorophenyl)methylamino	Isopropyl	(L)-1-Hydroxymethyl-2-methyl-propylamino
(4-Chlorophenyl)methylamino	Isopropyl	2-Hydroxy-2-phenyl-ethylamino
(4-Chlorophenyl)methylamino	Isopropyl	2-Amino-N1-(2-hydroxyethyl)ethylamino
(4-Chlorophenyl)methylamino	Isopropyl	2-Amino-N2-(2-hydroxyethyl)ethylamino
(4-Chlorophenyl)methylamino	Isopropyl	(S)-2-Phenyl-1-carboxamido-ethylamino
(4-Chlorophenyl)methylamino	Isopropyl	2-Amino-N2-(2-hydroxyethyl)-N1-(hydroxyethyl)ethylamino
(4-Sulfonamidophenyl)methylamino	Isopropyl	2-Aminoethylamino
(4-Fluorophenyl)methylamino	2-Oxo-3-butyl	Diethanolamino
(4-Fluorophenyl)methylamino	2-Oxo-3-butyl	2-Aminoethylamino
(4-Chlorophenyl)methylamino	2-Oxo-3-butyl	Diethanolamino
(4-Chlorophenyl)methylamino	2-Oxo-3-butyl	2-Aminoethylamino
(4-Methylphenyl)methylamino	Isopropyl	1-Hydroxymethyl-2-methyl-propylamino
(3-Methylphenyl)methylamino	Isopropyl	1-Hydroxymethyl-2-methyl-propylamino
(4-Chlorophenyl)methylamino	Isopropyl	2-(N2-dimethylamino)-N1-benzyl-ethylamino
(4-Chlorophenyl)methylamino	Isopropyl	1-Carboxamido-2-methyl-propylamino
(4-Chlorophenyl)methylamino	Isopropyl	2-Aminoethylamino
(4-Chlorophenyl)methylamino	Isopropyl	3-Aminopropylamino
(4-Chlorophenyl)methylamino	Isopropyl	5-Aminopentylamino
(4-Chlorophenyl)methylamino	Isopropyl	2-Amino-2-methyl-ethylamino
(4-Chlorophenyl)methylamino	Isopropyl	(S)-(+)-1-(Hydroxymethyl)propylamino
(4-Chlorophenyl)methylamino	Isopropyl	(R)-(-)-1-(Hydroxymethyl)propylamino
(4-Chlorophenyl)methylamino	Isopropyl	(S)-(+)-1-(Hydroxymethyl)ethylamino
(4-Chlorophenyl)methylamino	Isopropyl	(R)-(-)-1-(Hydroxymethyl)ethylamino
(4-Chlorophenyl)methylamino	Isopropyl	(S)-(+)-2-Hydroxypropylamino
(4-Chlorophenyl)methylamino	Isopropyl	(R)-(-)-2-Hydroxypropylamino
(4-Fluorophenyl)methylamino	Isopropyl	2-Amino-propylamino
(3-Chlorophenyl)methylamino	Isopropyl	Diethanolamino
(3-Chlorophenyl)methylamino	Isopropyl	2-Aminoethylamino
(2-Trifluoromethylphenyl)methylamino	Isopropyl	Diethanolamino
(2-Trifluoromethylphenyl)methylamino	Isopropyl	2-Aminoethylamino
(4-Chloro-3-trifluoromethylphenyl) methylamino	Isopropyl	Diethanolamino
(4-Chloro-3-trifluoromethylphenyl)	Isopropyl	2-Aminoethylamino

R_1X	R_2	R_3
methylamino		
(3,5-Dichlorophenyl)methylamino	Isopropyl	Diethanolamino
(3,5-Dichlorophenyl)methylamino	Isopropyl	2-Amino-ethylamino
(2-Trifluoromethyl-phenyl)methylamino	Isopropyl	2-(N2-dimethylamino)-N1-benzyl-ethylamino
(3-Chlorophenyl)methylamino	Isopropyl	Diethanolamino
(3-Chlorophenyl)methylamino	Isopropyl	2-Aminoethylamino
(2-Trifluoromethylphenyl)methylamino	Isopropyl	Diethanolamino
(2-Trifluoromethylphenyl)methylamino	Isopropyl	2-Aminoethylamino
(4-Chloro-3-trifluoromethylphenyl)methylamino	Isopropyl	Diethanolamino
(4-Chloro-3-trifluoromethylphenyl)methylamino	Isopropyl	2-Aminoethylamino
(3,5-Dichlorophenyl)methylamino	Isopropyl	Diethanolamino
(3,5-Dichlorophenyl)methylamino	Isopropyl	2-Aminoethylamino
(2-Trifluoromethylphenyl)methylamino	Isopropyl	2-(N2-Dimethylamino)-N1-benzylethylamino
(3-Chlorophenyl)methylamino	Isopropyl	2-(N2-Dimethylamino)-N1-benzylethylamino
(3,5-Dichlorophenyl)methylamino	Isopropyl	2-(N2-Dimethylamino)-N1-benzylethylamino
(4-Chloro-3-trifluoromethylphenyl)methylamino	Isopropyl	2-(N2-Dimethylamino)-N1-benzylethylamino
(4-Chlorophenyl)methylamino	Isopropyl	2-Amino-2-methylpropylamino
(4-Fluorophenyl)methylamino	Isopropyl	(S)-(2-Tetrahydrofuranyl)methylamino
(4-Fluorophenyl)methylamino	Isopropyl	(R)-(2-Tetrahydrofuranyl)methylamino
(4-Methylphenyl)methylamino	Isopropyl	Diethanolamino
(4-Fluorophenyl)methylamino	Isopropyl	2-Hydroxy-1-methylethylamino
(4-Fluorophenyl)methylamino	Isopropyl	(S)-2-Hydroxy-2-methylethylamino
(4-Fluorophenyl)methylamino	Isopropyl	(R)-2-Hydroxy-2-methylethylamino
(4-Fluorophenyl)methylamino	Isopropyl	1-Hydroxymethylpropylamino
(4-Flurophenyl)methylamino	Isopropyl	2-Amino-2-methylpropylamino

EXAMPLE 4

This Example describes a method for preparing compounds of this invention. The synthesis method disclosed in this Example is only slightly modified from that disclosed in Example 1.



The following compound was prepared according to the method above.

Preparation of 2,6-dichloro-9-isopropylpurine (4).

The 2,6-dichloropurine (5.00 g, 26.46 mmol) was suspended in 55 ml of dry DMF at room temperature and treated with sodium hydride, 60% dispersion (1.27 g, 31.75 mmol) added in portions. After stirring for 1 hr, 2-iodopropane (4.5 ml, 44.98 mmol) was added and the reaction stirred for 2 days. The reaction was poured into diethyl ether and washed once with saturated sodium bicarbonate solution and once with water. The mixture was dried over anhydrous sodium sulfate and concentrated in vacuo. The concentrate was chromatographed over silica gel eluting with 10% acetone in dichloromethane solution to give the desired N-9

alkylation product as a white solid.

Preparation of 2-chloro-6-(4-methylmercapto) anilino-9-isoproplypurine (5A).

2,6-Dichloro-9-isopropylpurine (0.15 g, 0.649 mmol) was dissolved in n-butanol (4 ml) and 4-(methylmercapato) aniline (0.089 ml, 0.714 mmol) and triethylamine (0.20 ml, 1.43 mmol) were added. The reaction mixture was heated at 80° overnight. The cooled reaction was diluted ethyl acetate and washed 1 x 1M HCl, 1 x saturated sodium bicarbonate, and 1 x brine before being dried with anhydrous sodium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel and eluting with 2% methanol in dichloromethane to give the desired product as a white solid.

Preparation of 2-diethanolamine-6-(4-methylmercapto) anilino-9-isopropylpurine (6A).

The purine (0.18 g, 539 mmol) was dissolved in N-methylyrrolidinone (3 ml) and diethanolamine (1 ml) and then heated at 120°C overnight. The cooled reaction was poured into diethyl ether and washed three times with water before drying over anhydrous sodium sulfate and concentrating in vacuo. The residue was chromatographed over silica gel eluting with 5% methanol in dichloromethane to give the desired product as an off-white solid. ^{1}H-NMR(δ, $CDCl_3$) : 8.08(s,1H), 7.58(d, 2H), 7.47(s,1H), 7.18(d, 2H), 4.95(br s, <2H), 4.52(m, 1H), 3.94(m, 4H), 3.83(m,4H), 2.43(s, 3H), 1.47(d, 6H).

Preparation of 4-(2-thienyl) benzonitrile.

Some R_1' groups must first be synthesized before reacting with the 2,6-dichloro-9-isopropylpurine. These groups can be synthesized through various coupling methods and other synthetic procedures known to those skilled in the art of organic synthesis.

To a pressure tube was added 4-bromobenzonitrile (0.20 g, 1.10 mmol), tetrakis(triphenylphosphine) palladium (0) (0.127 g, 0.1 eq) and 2-thiopheneboronic acid

(0.211 g, 1.65 mmol). The reaction was flushed under vacuum and flushed with dry nitrogen three times. Following flushes, ethyleneglycol dimethyl ether (5.5 ml) and an aqueous solution of sodium carbonate (2.53 ml, 1M) were added to the tube. The tube was then sealed and heated at 80°C overnight. The cooled reaction was the diluted with diethyl ether and washed twice with water before drying over sodium sulfate and concentrating in vacuo. The residue was chromatographed over silica gel eluting with 10% ethyl acetate in hexane to give the desired product as a white solid.

Preparation of 4-(2-thienyl) benzylamine.

The 4-(2-thienyl)benzonitrile (0.086 g, 0.464 mmol) was dissolved in dry tetrahydrofuran (1.6 ml) before lithium aluminum hydride (0.46 ml, 0.464 mmol, 1 M in THF) was added dropwise. The reaction was allowed to stir at room temperature overnight. TLC (5% methanol in dichloromethane) still showed starting material remaining. Another 1 eq of LAH was added. After an additional hour, the reaction was quenched by the Fieser and Fieser method using wager (17.46µl), aqueous sodium hydroxide solution (17.46µl, 15% soln.), and water (52.37 µl) added sequentially to the reaction. The reaction was then diluted with diethyl ether and water and extracted twice with diethyl ether before drying over sodium sulfate and concentrating in vacuo. The residue was carried on crude without any further purification.

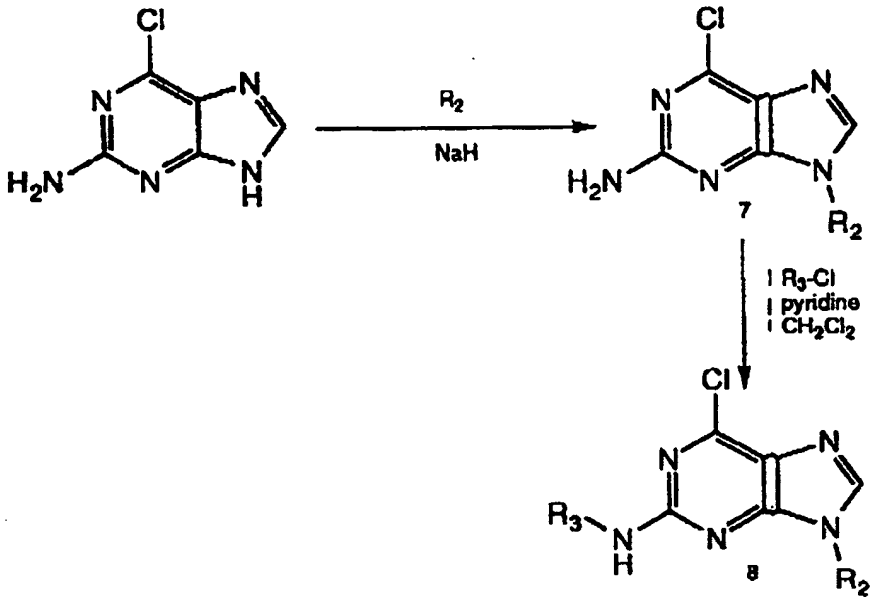
Table 3 below identified compounds of this invention that were prepared according to the general synthesis method set forth in this Example.

Table 4
Compounds Prepared By The Method of Example 4

R_1'-X	R2	R3
Cl	Me	Cl
ethanolamino	Me	ethanolamino
cyclopropylmethylamino	isopropyl	Cl
cyclopropylmethylamino	isopropyl	diethanolamino
3,5-dinitroanilino	isopropyl	Cl
3-phenoxyanilino	isopropyl	Cl
4-iodoanilino	isopropyl	Cl
3-aminoquinolino	isopropyl	Cl
3,5-dinitroanilino	isopropyl	diethanolamino
Cl	epoxymethyl	Cl
4-methoxybenzylamino	2,3-dihydroxypropyl	diethanolamino
4-phenylanilino	isopropyl	diethanolamino
4-phenylbenzylamino	isopropyl	Cl
2-naphthalenylmethylamino	isopropyl	Cl
1-naphthalenylmethylamino	isopropyl	Cl
2-phenylbenzylamino	isopropyl	Cl
3-quinolinylamino	isopropyl	diethanolamino
5-quinolinylamino	isopropyl	diethanolamino
6-quinolinylamino	isopropyl	diethanolamino
8-quinolinylamino	isopropyl	diethanolamino
n-butylamino	isopropyl	Cl
4-(2-thiophenyl)benzylamino	isopropyl	deithanolamino
4-(2-thiophenyl)benzylamino	isopropyl	Cl
3-thiomethoxyanilino	isopropyl	Cl
4-thiomethoxyanilino	isopropyl	Cl
3-thiomethorxyanilino	isopropyl	diethanoamino
4-thiomethoxyanilino	isopropyl	diethanoamino
4-(2-pyridinyl) benzylamino	isopropyl	Cl
3-methoxybenzylamino	isopropyl	Cl
3,4-dimethoxybenzylamino	isopropyl	Cl
3,4,5-trimethoxyenzylamino	isopropyl	Cl
3-methoxybenzylamino	isopropyl	diethanolamino
3,4-dimethoxybenzylamino	Isopropyl	diethanolamino
3,4,5-trimethoxbenzylamino	Isopropyl	diethanolamino
4-(3-thiophenyl)benzylamino	Isopropyl	Cl
4-(4-methoxphenyl) benzylamino	Isopropyl	Cl
4-(4-bromophenyl) benzylamino	Isopropyl	diethanolamino
4-(3- methoxyphenyl) benzylamino	Isopropyl	diethanolamino
4-(4-methoxypheny) benzylamino	Isopropyl	diethanolamino
4-(3-thiophenyl) benzylamino	Isopropyl	diethanolamino
4-(3-methylpheny) benzylamino	Isopropyl	Cl
4-(4-methylphenyl) benzylamino	Isopropyl	Cl
4-(4-trifluoromethylphenyl) benzylamino	Isopropyl	Cl
3-(4 nitrilophenyl)anilino	Isopropyl	Cl
3-(4-nitrilophenyl)anilino	Isopropyl	diethanolamino
4-(2-pyridinyl)benzylamino	Isopropyl	Cl
4-(2-pryidinyl)benzylamino	Isopropyl	diethanolamino

EXAMPLE 5

This Example describes a method for preparing compounds of this invention. The synthesis method disclosed in this Example is only slightly modified from that disclosed in Example 1.



The following compound was prepared according to the method above.

Preparation of 2-amino-6-chloro-9-methylpurine (7).

The 2-amino-6-chloropurine (1.08 g, 6.4 mmol) was suspended in dry DMF (75 ml) and treated with sodium hydride, 60% dispersion (0.28 g, 7 mmol). The suspension was stirred for 15 min before iodomethane (0.44 ml, 7.06 mmol) was added and the resulting yellow solution stirred for 1 hr 45 min. The solid was filtered and the filtrate evaporated before addition of water for 10 min. The resulting solid was filtered and dried overnight to

give the product as a mixture of N-7 and N-9 alkylation products. The residual liquor was left overnight and more crystals were collected the next day and dried.

Preparation of 6-chloro-2-(2-methoxyacetylamino)-9-methylpurine (8).

The mixture of isomers from above was dissolved in dichloromethane and pyridine (2 eq) followed by treatment with methoxyacetyl chloride (4 eq). The reaction was stirred at room temperature until complete. The reaction was evaporated and filtered through a plug of silicia gel eluting with 2% methanol in dichloromethane followed by purification on a chomatotron using silica gel and eluting with 2% methanol in dichloromethane to isolate the desired product.

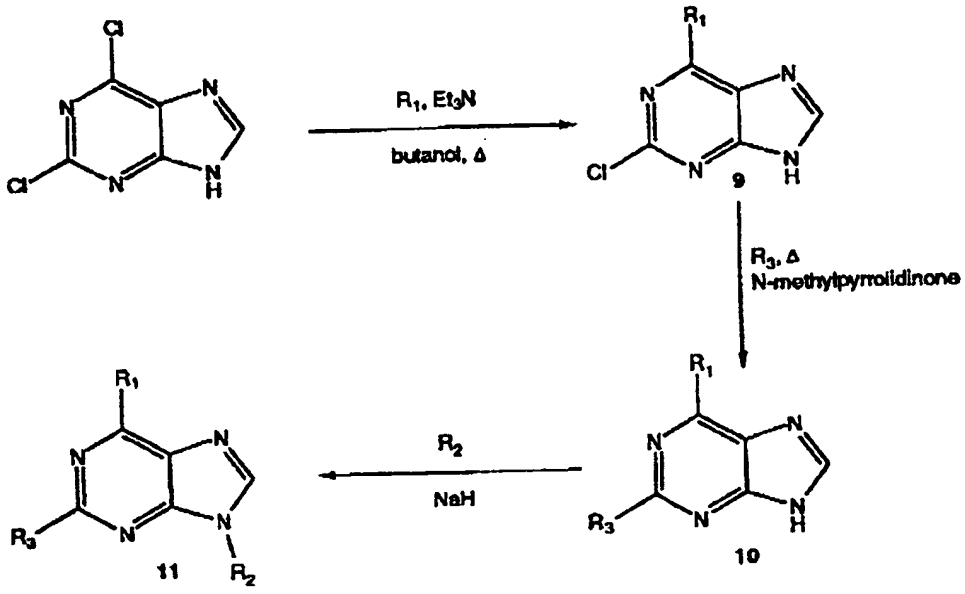
Table 5 identifies compounds of this invention that were prepared according to the synthesis method set forth in this Example.

Table 5
Compounds Prepared By The Method of Example 5

R1	R2	R3
Cl	Me	H
Cl	Me	2-methoxyacetylamino

EXAMPLE 6

This Example describes a method for preparing compounds of this invention. The synthesis method disclosed in this Example is only slightly modified from that disclosed in Example 1.



The following compound was prepared according to the method above.

Preparation of 2-chloro-6-(4-phenyl benzylamino) purine (9).

The 2,6-dichloropurine (5.0 g, 26.45 mmol) was suspended in n-butanol (50 ml) and the 4-phenylbenzylamine (6.61 g, 29.1 mmol) and triethylamine (4.1 ml, 29.1 mmol) were added. The solution was heated at 120°C overnight then cooled. Filtered off product using excess n-butanol and washed precipitate with 100 ml 1M HCl and 200 ml water. The solid was dried in vacuum over overnight at 70°C to give the desired product as a pale yellow solid

Preparation of 2-diethanolamino-6-(4-phenyl benzylamino) purine (10).

The 2-chloro-6-(4-phenyl benzylamino) purine (2.0 g, 5.96 mmol) was added together with diethanolamine (11.4 ml, 119.2 mmol) and N-methylpyrrolidinone (10 ml) and heated at 120°C overnight. The cooled reaction was poured into dichloromethane and washed twice with water. The organic layer was dried with anhydrous sodium sulfate and concentrated in vacuo to give the desired product as a pale green solid which was further dried in vacuum oven at 70°C for 2 days.

Preparation of 2-diethanolamino-6-(4-phenyl benzylamino)-9-methylpurine (11).

The 2-diethanolamino-6-(4-phenyl benzylamino) purine (0.050 g, 0.124 mmol) was dissolved in dry DMF and treated wit sodium hydride, 60% dispersion (5.5 mgs, 0.136 mmol) for 1 hr. iodomethane (0.009 ml, 0.148 mmol) was added and the resultant solution stirred at room temperature overnight. Poured reaction into diethyl ether and washed twice with saturated sodium bicarbonate solution before drying over anhydrous sodium sulfate and concentrating in vacuo. The residue was chromatographed over silica gel eluting with 5% methanol in dichloromethane to give the produce as a white solid.

$_1$H-NMR(δ, CDCl3): 7.55 (m,4H), 7.41 (m, 4H) 7.35(m, 4H), 6.41 (br s, < 1H), 5.10(br s, <2H), 4.72 (br s, 2H), 3.86 (m, 4H), 3.74(m, 4H), 3.59(s, 3H).

Table 5 identified compounds of this invention that were prepared according to the synthesis method set forth in this Example.

Table 6
Compounds Prepared By The Method of Example 6

R_1'-X	R2	R3
4-phenylbenzylamino	Methyl	diethanolamino
4-phenylbenzylamino	Cyclopentyl	diethanolamino
4-phenylbenzylamino	Allyl	diethanolamino
4-phenylbenzylamino	Benzyl	diethanolamino
4-phenylbenzylamino	3-methylbutyl	diethanolamino
4-phenylbenzylamino	Isobutyl	diethanolamino

4-phenylbenzylamino	t-butylacetate	diethanolamino
4-phenylbenzylamino	Methylacetate	diethanolamino
4-phenylbenzylamino	Cyclobutyl	diethanolamino
4-phenylbenzylamino	Ethyl	diethanolamino
4-phenylbenzylamino	Propyl	diethanolamino

EXAMPLE 7

Composition of this invention were evaluated in the following assays.

CDK2 assays:

Compositions of this invention were assayed to determine their CDK2 inhibitory activity. The assay system (total volume of 50 µl) contained 50 mM Tris-Cl, pH 7.4, 10 mM $MgCl_2$, 5 mM DTT, 1 µg of histone H1, 30 µM ATP (1 µCi of gamma^{32}P labeled ATP), 10 µg of BSA and 1 ng of purified CDK2. After incubation at 30°C for 30 min, the reaction was terminated by the addition of 10 µl of 10% TCA and the samples were blotted onto to nitrocellulose filters. These filters were washed extensively in 10% TCA and assayed for radioactivity. Blanks contained no enzyme. To ascertain the potency of various compounds of this invention, the compounds were added to the above assay at concentrations ranging from 100 to 0.02 µg/ml. After incubation at 30 min., the assay tubes were processed as above. In all assays, various concentrations of olomoucine were added and were used as a standard positive control. The IC_{50} (enzyme) listed in Table 7 is defined as the concentration required to inhibit CDK2 activity by 50%.

EXAMPLE 8

Cell Proliferation Assays:

Early passage rat aortic smooth muscle cells (CV Therapeutics Cell repository) were seeded in 48 well dishes (Falcon, ml/well) at a density of 20,000 cells/ml of DME containing 5% heat inactivated bovine serum. The cells were incubated in a standard tissue culture incubator for 48 hr. The medium was aspirated and the wells were replenished with 0.2 ml of fresh medium. Compounds of this invention were added at concentrations ranging from 100 to 0.37 µg/ml. After 48 hr incubation, the medium was aspirated and the cultures were treated with 0.2 ml of saline 0.25 µl of phenozine methosulfate solution containing MTS (Cell Titer 96® Aqueous Non-radioactive cell proliferation assay kit, Catalog # G 5430, Promega, 2800 Woods Hollow Road, Madison, WI 53711-5399). The IC_{50} cells listed in Table 6 is defined as the concentration required to inhibit cell proliferation by 50%. Olomoucine at various concentrations was added and was used as a standard positive control.

TABLE 7
Bioactivity of Selected Representatives of this Invention

R_1'-X	R2	R3	IC_{50} (µg/mL) enzyme	IC_{50} (µg/mL) cells
benzylamino	Me	Ethanolamino	7	70
4-methoxybenzylamino	H	Cl	60	NA
4-methoxybenzylamino	Me	Cl	6	>70
4-methoxybenzylamino	Me	Ethanolamino	4	48
4-chlorobenzyloxy	H	Cl	60	NA
4-chlorobenzyloxy	Me	Cl	60	NA
4-chlorobenzyloxy	trifluoromethyl	Cl	>60	NA
4-methoxybenzylamino	isopropyl	Cl	4	77

R_1'-X	R2	R3	IC_{50} (μg/mL) enzyme	IC_{50} (μg/mL) cells
4-methoxybenzylamino	isopropyl	Ethanolamino	4	43
4-methoxybenzylamino	Me	Diethanolamino	4	48
4-methoxybenzylamino	2-methylpropyl	Cl	60	>70
ethanolamino	Me	Ethanolamino	>60	>70
4-methoxybenzylamino	trifluoromethyl	Cl	>60	>70
4-methoxybenzylamino	benzyl	Cl	>60	>70
ethanolamino	H	Benzylamino	>60	NA
4-methoxybenzylamino	isopropyl	Diethanolamino	0.2	2.1
4-methoxybenzylamino	perfluoroisopropyl	Cl	>45	NA
4-methoxybenzylamino	perfluoroisopropyl	Diethanolamino	40	NA
4-methoxybenzylamino	ispropyl	3-pyrroline	1	12.5
4-methoxybenzylamino	hydroxyethyl	Diethanolamino	0.5	62
4-methoxybenzylamino	isopropyl	Serinol	0.4	15
4-methoxybenzylamino	isopropyl	1,3-diamino-2-hydroxypropane	0.6	25
4-methoxybenzylamino	3-cyanopropyl	Cl	>60	NA
4-methoxybenzylamino	3-chloropropyl	Cl	>60	NA
4-methoxybenzylamino	benzyl	Cl	>60	NA
4-methoxybenzylamino	Methyl 4-carboxybenzyl	Cl	>60	NA
4-methoxybenzylamino	Naphthaloylethyl	Cl	>60	NA
4-chlorobenzylamino	Trifluoromethyl	Cl	1	NA
4-methoxybenzylamino	isopropyl	N-(2-cyanopropyl)-N-(3-pyridylmethyl)-amino	1	NA
4-methoxybenzylamino	isopropyl	2-(hydroxymethyl)-3-methylbutan-2-amino	1	NA
4-methoxybenzylamino	isopropyl	3-hydroxypiperidino	1	NA
cyclohexylmethylamino	isopropyl	Cl	1	NA
piperonylamino	isopropyl	Diethanolamino	0.8	NA
4-methoxybenzylamino	isopropyl	Diisopropanolamino	0.8	NA

R_1'-X	R2	R3	IC_{50} (μg/mL) enzyme	IC_{50} (μg/mL) cells
anilino	isopropyl	Cl	1	NA
4-methoxybenzylamino	isopropyl	N-benzyl-N-2-hydroxyethylamino	1	NA
4-phenylanilino	isopropyl	Diethanolamino	0.6	NA
4-phenylbenzylamino	isopropyl	Diethanolamino	0.6	NA
4-phenylbenzylamino	isopropyl	3-amino-1,2-propanediol	0.6	NA
4-(2-thiophenyl)benzylamino	isopropyl	Diethannolamino	0.5	NA
4-(4-methylphenyl) benzylamino	isopropyl	Diethanolamino	0.6	NA
4-(4-trifluoromethylphenyl) benzyalmino	isopropyl	Diethanolamino	0.6	NA
4-thiomethoxyanilino	isopropyl	Cl	0.6	NA
3-(4-nitrilophenyl) anilino	isopropyl	Diethanolamino	0.5	NA
3-thiomethoxyanilino	isopropyl	Diethanolamino	0.1	NA
4-thiomethoxyanilino	isopropyl	Diethanolamino	0.07	NA
3-methoxybenzylamino	isopropyl	Cl	0.9	NA
4-(2-pyridinyl) benzylamino	isopropyl	Diethanolamino	0.16	NA
3-methoxybenzylamino	isopropyl	Diethanolamino	0.5	NA
(4-Chlorophenyl)methylamino	Isopropyl	Diethanolamino	0.12	0.3
(4-Fluorophenyl)methylamino	Isopropyl	Diethanolamino	0.15	2.2
(4-Trifluoromethylphenyl) methylamino	Isobutyl	Diethanolamino	59	NA
(4-Trifluoromethylphenyl) methylamino	Isopropyl	Diethanolamino	0.56	NA
(4-Chlorophenyl)methylamino	Isopropyl	(S)-2-Amino-3-phenylpropylamino	1.07	NA
(4-Fluorophenyl)methylamino	Isopropyl	2-Aminoethylamino	0.17	1.4
(4-Fluorophenyl)methylamino	Isopropyl	(D)-1-Hydroxymethyl-2-methyl-propylamino	0.06	2.7
(4-Fluorophenyl) methylamino	Isopropyl	(L)-1-Hydroxymethyl-2-	0.19	NA

R_1'-X	R2	R3	IC_{50} (μg/mL) enzyme	IC_{50} (μg/mL) cells
		methyl-propylamino		
(4-Chlorophenyl)methylamino	Isopropyl	(D)-1-Hydroxymethyl-2-methyl-propylamino	0.19	NA
(4-Chlorophenyl)methylamino	Isopropyl	(L)-1-Hydroxymethyl-2-methyl-propylamino	0.05	NA
(4-Chlorophenyl)methylamino	Isopropyl	2-Hydroxy-2-phenyl-ethylamino	0.08	>5
(4-Chlorophenyl)methylamino	Isopropyl	2-Amino-N1-(2-hydroxyethyl)ethylamino	0.07	0.2
(4-Chlorophenyl)methylamino	Isopropyl	2-Amino-N2-(2-hydroxyethyl)ethylamino	2.02	NA
(4-Chlorophenyl)methylamino	Isopropyl	(S)-2-Phenyl-1-carboxamido-ethylamino	1.07	NA
(4-Chlorophenyl)methylamino	Isopropyl	2-Amino-N2-(2-hydroxyethyl)-N1-(hydroxyethyl)ethylamino	0.43	NA
(4-Sulfonamidophenyl)methylamino	Isopropyl	2-Aminoethylamino	9	NA
(4-Fluorophenyl)methylamino	2-Oxo-3-butyl	Diethanolamino	11	NA
(4-Chlorophenyl)methylamino	2-Oxo-3-butyl	Diethanolamino	37	NA
(4-Chlorophenyl)methylamino	Isopropyl	2-Aminoethylamino	0.35	0.1
(4-Chlorophenyl)methylamino	Isopropyl	3-Aminopropylamino	1.0	NA
(4-Chlorophenyl)methylamino	Isopropyl	5-Aminopentylamino	31	NA
(4-Chlorophenyl)methylamino	Isopropyl	2-Amino-2-methyl-ethylamino	0.05	0.1
(4-Chlorophenyl)methylamino	Isopropyl	(S)-(+)-1-(Hydroxymethyl)propylamino	0.17	NA
(4-Chlorophenyl)methyla	Isopropyl	(R)-(-)-1-(Hydroxymethyl)pr	0.18	NA

R_1'-X	R2	R3	IC_{50} (μg/mL) enzyme	IC_{50} (μg/mL) cells
mino		opylamino		
(4-Chlorophenyl)methylamino	Isopropyl	(S)-(+)-1-(Hydroxymethyl)ethylamino	0.26	NA
(4-Chlorophenyl)methylamino	Isopropyl	(R)-(-)-1-(Hydroxymethyl)ethylamino	0.35	NA
(4-Chlorophenyl)methylamino	Isopropyl	(S)-(+)-2-Hydroxypropylamino	0.38	NA
(4-Chlorophenyl)methylamino	Isopropyl	(R)-(-)-2-Hydroxypropylamino	0.43	NA
(4-Fluorophenyl)methylamino	Isopropyl	2-Amino-propylamino	0.48	NA
(4-Fluorophenyl)methylamino	Isopropyl	(S)-(2-Tetrahydrofuranyl)methylamino	0.63	NA
(4-Fluorophenyl)methylamino	Isopropyl	(R)-(2-Tetrahydrofuranyl)methylamino	0.58	NA
(4-Fluorophenyl)methylamino	Isopropyl	2-Hydroxy-1-methylethylamino	0.18	NA
(4-Fluorophenyl)methylamino	Isopropyl	(S)-2-Hydroxy-2-methylethylamino	0.22	NA
(4-Fluorophenyl)methylamino	Isopropyl	(R)-2-Hydroxy-2-methylethylamino	0.23	>5
(4-Fluorophenyl)methylamino	Isopropyl	1-Hydroxymethylpropylamino	0.11	2.4

The inhibition of cell proliferation properties of the compounds of this invention are demonstrated by their ability to inhibit cell proliferation in the range of about 0.05 μg/ml to 100 μg/ml, preferably less than 0.5 μg/ml.

Similar assays were performed using the following cell lines; P388 – mouse lymphoid neoplasm; L1210 – mouse lymphcytic leukemia; Caco2 human colon adenocarcinoma; MCF7 human breast adenocarcinoma; PupVSMC rat neonatal aortic smooth muscle cells; Ovcar human ovarian Carcinoma; Panc1 human pancreatic adenocarcinoma; and HUVEC human

umbilical cord endothelial cells. The inhibitory activity of several compositions of this invention against one or more of the cell lines are reported in Tables 8 and 9 below.

Table 8

IC_{50} (μg/ml) for Inhibition of Cell Proliferation

R_1X	R_2	R_3	P 388	L 120	Caco 2	MCF 7	Panc1	OvCar	PupVSMC	HUVEC
(4-methoxyphenyl)-methylamino	Isopropyl	Diethanolamino	1.5	2.5	4.5	8.0	10.0	11.0	0.5	3.0
(4-phenylphenyl)amino	Isopropyl	Diethanolamino	1.0	4.0	0.5	4.0	4.0	7.0	1.0	
(4-phenylphenyl)-methylamino	Isopropyl	Diethanolamino	< 1.0	1.0	3.5	1.0	1.3	2.0		
(4-methoxyphenyl)-methylamino	Isopropyl	Morpholino	>5				5.5	4.0		
3-phenoxyphenyl,3-benzyloxyphenyl	isopropyl	Diethanolamino	1.5			2.0	2.5	2.0		

Table 9

R_1X	R_2	R_3	MRC-5	PupVSMC
(4-methoxyphenyl)methylamino	Isopropyl	Diethanolamino	5	0.4
(4-Chlorophenyl)methylamino	Isopropyl	2-Aminoethylamino	1	0.1
(4-Chlorophenyl)-methylamino	Isopropyl	2-Amino-2-methylethylamino	1	0.1
(4-Chlorophenyl)-methylamino	Isopropyl	2-Amino-N1-(2-hydroxyethyl)ethylamino	1	0.3
(4-Chlorophenyl)-methylamino	Isopropyl	Diethanolamino	3	0.3

MRC-5 = Human Fibroblast

PupVSMC = Rat neonatal aortic smooth muscle cells

EXAMPLE 8

Compounda of this invention was evaluated for effectiveness using the Murine Leukemia Model. The Murine Leukemia Model is a standard model used in the evaluation of antitumor agents. CDF1 mice were injected ip with L1210 cells ($1x10^3$ cells/mouse). Twenty-four hours later, these mice were treated with various doses (ip) of compound 3 of Example 1 in saline. The dosing regimen used in this study is outlined in Table 10, below. Mice were dosed with compound 3 daily or on alternate days. Control mice received saline. After 7 days, dosing was suspended and survival monitored.

Table 10

Treatment		**N**	**Median survival time Days**	**T/Cx100**
Saline control		7	10 (9-13)	100
Compound 3	0.5 mg/kg bid	7	11 (10-15)	110
	1.0 mg/kg bid	7	13 (11-13)	130
	2 mg/kg bid	7	12 (10-14)	120
	4 mg/kg - days 1,3,5,7	7	13 (10-15)	130
	8 mg/kg - days 1,3,5,7	7	13 (12-16)	130

The results indicate that rats administered compound 3 survived longer than the control rats.

EXAMPLE 9

This example measured the effect of an acute local delivery of compound 3 of Example 1 in reducing neointima formation following balloon angioplasty in the rat carotid artery model. In this example, the left common carotid arteries of adult male rats (n=10 per experimental group) were surgically injured using a Fogarty arterial embolectomy catheter. Immediately after injury, the common carotid artery was bisected with a vascular clamp, thereby establishing an untreated and treated segment. A drug delivery catheter was then inserted into the distal half of the common carotid. After drug delivery, the catheter was removed and excess drug was washed out by removing the vascular clamp and re-establishing blood flow before closing the artery. The animals were allowed to recover for 14 days before harvesting the common carotid artery. The harvested tissue was sectioned and the neointimal area was digitized and measured with a computer planimetery system. For each animal, 15 measurements were averaged for the untreated segment and 15 for the treated. {2-[(2-aminoethyl)amino]-9-(methylethyl)purin-6-yl}[(4-chlorophenyl)methyl]amine was administered at a dose of 5 mg/mL reducing the neointimal area about 90% in comparison to the 6% reduction of saline alone.

The results of this Example are found in Figure 1. According to Figure 1, administering compound 3 of Example 1 to a damaged carotid artery reduced the neointimal area about 88% in comparison to the 6% reduction produced by the saline vehicle alone.

EXAMPLE 10

IκB-α Kinase Assays:

Compositions of this invention were assayed to determine their IκB-α kinase inhibitory activity. The human umbilical vein endothelial cell line (HUVEC) used in these studies was purchased from Clonetics (San Diego, CA) and was maintained in endothelial cell growth medium supplemented with 2% fetal bovine serum, 10ng/ml human recombinant epidermal growth factor, 1 μg/ml hydrocortisone, 50 μg/ml gentamicin, 50 ng/ml amphotericin B and 12 μg/ml bovine brain extract at 37°C in a tissue culture incubator. All growth media and supplements were purchased from Clonetics (San Diego, CA). *E. coli* lipopolysaccharide (LPS) serotype 0111:B4 was purchased from Sigma (Saint Louis, Ml). All other chemicals were of reagent grade.

Preparation of cell Lysate: Monolayers (75 cm^2) of HUVEC cells were treated with LPS (100 ng/ml) for 5 minutes after which the cell media was rapidly removed and the monolayer washed three times with ice cold PBS. The cell layer was scraped into 10 ml PBS and the cells pelleted by centrifugation (3000 rpm, 5 min, 4°C). Cell lysate was prepared by incubating the cell pellet in 0.2 ml lysis buffer (20mM HEPES, pH7.3, 50mM NaCl, 10mM $MgCl_2$, 1mM EDTA, 1mM EGTA, 1mM sodium orthovanadate, 10mM β-glycerophospate, 1mM phenylmethylsulfonylfuoride, 1mM dithiothreitol, 0.5% Nonidet P-40 for 15 minutes at 37°C for frequent vortexing. Cell debris was removed from the sample by microcentrifugation (10,000xg, 15 minutes, 4°C) and the supernatant was "precleared" by the addition of 100 ml of a suspension of sepharose 4B in lysis buffer and mixing gently for 1 hour at 4°C. The speharose 4B beads were removed by microcentrifugation and the supernatant aliquotted and stored at 80°C.

Solid Phase IκB-α kinase assay: 1 μg of GST- IκB-α, corresponding to full length IκB-α of human origin, (Santa Cruz Biotechnology,) was incubated with 20 μl of a 50% slurry of glutathione S sepharose 4B (Pharmacia) in reaction buffer (20mM HEPES, pH7.3, 10mM $MgCl_2$, 15mM β-glycerophosphate, 0.5mM sodium orthovanadate, 0.5mM EGTA) for 30 minutes at room temperature. The GST- IκB-bead complex was the washed three times with 0.5 ml of reaction buffer by resuspension and microcentrifugation. 10μg of HUVEC cell lysate protein in 100μl of reaction buffer was then added to the GST- IκB-bead complex and the mixture incubated with gentle mixing at 4°C for 1 hour. The bead complex was then washed three times with reaction buffer containing 0.2 M NaCl and once with reaction buffer alone. Finally the bead complex was resuspended in 20μl of reaction buffer containing 5μCi [y-^{32}P]ATP (>5000 ci/mmol, New England Nuclear Corp. Boston, MA) and incubated at room temperature for 15 minutes. The reaction was terminated by the addition of 10μl of SDS-PAGE sample buffer and boiled for 3 minutes before separation by SDS-PAGE (10-20% gradient Readygel, BioRad). Following electrophoresis the gel was fixed (50% methanol 10% acetic acid) for 15 minutes, washed three times for 5 minutes each with distilled H_20 and treated with 5% glycerol for 15 minutes before drying down and exposing to film for autoradiography (X-OMAT XAR-5 Kodak).

In gel kinase assay: IκB-α isozymes were assayed for activity using a modification of previously published methods (11, 19, 20). Briefly duplicate samples of the IκB-glutathione sepharose 4B bead complex were prepared as described above and were separated by electrophoresis through a 12% SDS-PAGE gel which had been polymerised in the presence of 15 μg/ml GST- IκB-α. Following electrophoresis the gel was washed gently twice for 30 minutes each with 50mM Tris-HCl pH8.0, 5mM β-mercaptoethanol; 20% isopropanol to

remove SDS. Proteins were then denatured within the gel by incubation for 45 minutes in 100ml 50mM Tris-HCl pH8.0; 5mM β-mercaptoethanol; 0.04% Tween 40. The gel was then cut in half to separate the duplicate samples, one half was incubated in 10 ml reaction buffer alone and the other in 10 ml reaction buffer containing 10μg/ml of 2-diethanolamino-6(4-phenyl anilino)-9-isopropyl purine (compound 6 of Example 2) for 1 hour at room temperature which 10μCi[y-^{32} P]ATP was added and the incubations continued for a further hour at room temperature. The gels were then subjected to multiple 15 minute washes of 100ml each 5% trichloroacetic acid containing 1% sodium pyrophosphate until 1 ml of wash solution gave close to background radioactivity. The gels were then dried down and exposed to file for autoradiograhy.

Preparation of 2-diethanolamino-6-(4-phenybenzylamino)-9-isopropyl purine Epoxy activated Sepharose 6B Affinity Matrix. Freeze dried epoxy activated Sepharose 6B (Pharmacia LKB, Piscataway, NJ) was chosen for the coupling reaction due to its ability to form an ether bond between an hydroxyl-containing ligand and the epoxide group on the sepharose. The gel was swollen according to the manufacturer's instructions, (100mg) of compound 6 of Example 2 was dissolved in 1ml coupling solution (1.2:1 v/v dimethylformamide : 0.1N NaOH) and mixed with 0.5ml of swollen gel at pH 10-11 for 72 hours at room temperature with gentle agitation. Excess reactive groups were blocked with 1M ethanolamine for 4 hours at 50°C and the gel slurry was poured into 1 ml syringe column. The resin was activated with three alternating cycles of twenty column volumes each of pH 4.0 (0.1M acetate, 0.5M NaCl) and pH 8.0 (0.1M Tris-HCl, 0.5M NaCl) buffers followed by twenty column volumes of reaction buffer (20mM HEPES, pH7.3, 10mM $MgCl_2$, 15mM β-glycerophophate, 0.5mM sodium orthovanadate, 0.5mM EGTA). The column was stored at 4°C in reaction buffer containing

0.5% sodium azide and regenerated prior to each use with alternating cycles of low and high pH as described above.

Activated HUVEC cell lysate (500μg protein in 1ml reaction buffer) was passed over the CVT-1545 sepharose matrix sequentially five times and the flow through was saved (unbound material). The matrix was then washed three times with 1ml of reaction buffer (wash 1-3) then three times each with reaction buffer containing 0.5M NaCl (eluate 1-3). Aliquots (20μl from 1ml) of each sample were assayed for their ability to phosphorylate at GST- IκB-sepharose bead complex and analyzed by SDS-PAGE as described above.

Assay of affinity enriched IκB-α kinase. The bulked 0.5 M NaCl eluates from the affinity matrix were used as the source of enzyme for development of an IκB-α kinase filter assay. Each reaction contained affinity enriched IκB-α kinase (1μg protein), 10ng GST IκB-α kinase and 0.5μCi[y-^{32}P]ATP (>5000 Ci/mmol, New England Nuclear Corp, Boston, MA) in 20μl reaction buffer. The reaction was incubated for 15 minutes at room temperature and was terminated by the addition of 2μl 0.5M EDTA. Reaction mixtures were blotted onto phosphocellulose disks (Gibco BRL Life Technologies, Gaithersburg, MD) and the filters washed three times with 0.15M phosphoric acid with gentle shaking for 15 minutes (up to ten filters were washed with 300 ml of 0.15M phosphoric acid.) Following a third wash the filters were air dried, added to scintillation fluid and assayed by liquid scintillation spectrometry.

Electrophoretic Mobility Shift Assay: Nuclear extracts were prepared using a high-salt buffer extraction procedure. 10 pmol of double stranded NF-κB consenses oligonucleotide (5'-AGTTGAGGGGACTTTCCCAGGC-3'))Promega) was 5' end labeled with 5μCi [y-^{32}P]ATP (>5000 Ci/mmol, New England Nuclear Corp, Boston, MA) by incubaton with T4 polynucleotide kinase for 1 hr at 37°C. Unincorporated nucleotides were removed by pasing

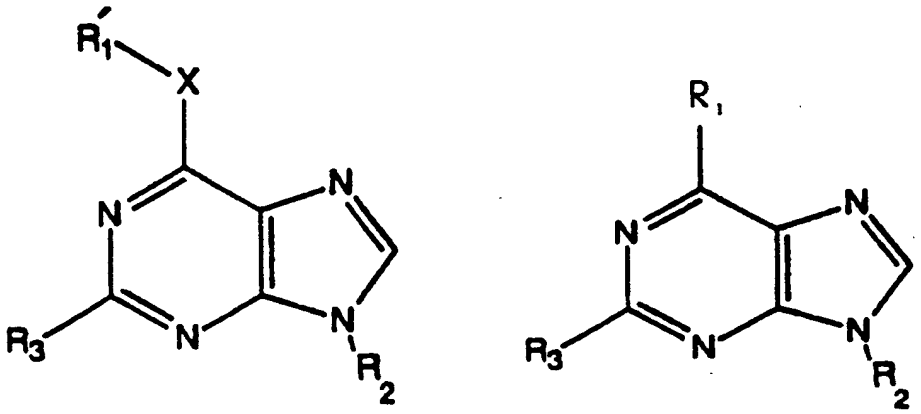
the reaction mixture over 1ml Sephadex G-5-spin column. Binding assays were performed at room temperature for 1 hr and consisted of 10μg nuclear extract protein, 1μg salmon sperm DNA, and $5x10^4$ cpm of ^{32}P labeled consensus of oligonucleotide in the presence and absence of fifty fold unlabeled oligonucleotide. DNA-protein complexes were resolved by 8% non denaturing polyacrylamide gel electrophoresis, the gels were dried onto filter paper and visualized by autoradiography.

Table 11
Enzyme Activity of Selected Representatives of this Invention

R_1'-X	R2	R3	IC50(μM) enzyme
4-phenylbenzylamino	Isopropyl	Diethanolamino	1.1
4-phenylbenzylamino	Isopropyl	Diethylamino	>2.4
4-phenylbenzylamino	Isopropyl	Ethanolamino	2.5
4-bromoanilino	Isopropyl	Diethanolamino	14
4-(3-methoxphenyl) benzylamino	Isopropyl	Diethanolamino	>10
4-(4-methoxphenyl) benzylamino	Isopropyl	Diethanolamino	11
3-(4-nitrilophenyl) anilino	Isopropyl	Diethanolamino	2.2
4-thiomethoxyanilino	Isopropyl	Diethanolamino	12.4
4-(2-pyridinyl) benzylamino	Isopropyl	Diethanolamino	4.5

What we claim is:

1. A 2,6,9-trisubstituted purine composition of matter having the following formula:



(I)

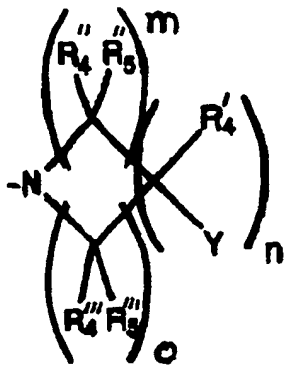
wherein R_1 is halogen or R'_1-X wherein X = NH, O, S, $S(O_2)$.

R'_1 is alkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkenyl, and alkynyl, each having one to 20 carbon atoms, which alkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkenyl, and alkynyl, are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, aryl, CF_3, heteroaryl, heterocyclyl, R^{22}, SR^{20}, $S(O)R^{21}$, SO_2R^{21}, $SO_2NR^{20}R^{23}$, $SO_2NR^{20}COR^{21}$, $SO_2NR^{20}CONR^{20}R^{23}$, $SO_2NR^{20}CO_2R^{21}$, $NR^{20}R^{23}$, $NR^{20}COR^{21}$, $NR^{20}CO_2R^{21}$, $NR^{20}CONR^{20}R^{23}$, $N(R^{20})C(NR^{20})NHR^{23}$, $NR^{20}SO_2R^{21}$, OR^{20}, $OCONR^{20}R^{23}$, $OCONR^{20}SO_2R^{21}$, $OCONR^{20}R^{23}$, CN, CO_2R^{20}, $CONR^{20}R^{23}$, $CONR^{20}SO_2R^{21}$ and COR^{20};

R_2 is a hydrogen or hydrocarbon selected from the group alkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkenyl,and alkynyl, each having one to 20 carbon atoms,

which alkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkenyl,and alkynyl,are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, aryl, heteroaryl, heterocyclyl, R^{22}, SR^{20}, $S(O)R^{21}$, SO_2R^{21}, $SO_2NR^{20}R^{23}$, $SO_2NR^{20}COR^{21}$, $SO_2NR^{20}CONR^{20}R^{23}$, $SO_2NR^{20}CO_2R^{21}$, $NR^{20}R^{23}$, $NR^{20}COR^{21}$, $NR^{20}CO_2R^{21}$, $NR^{20}CONR^{20}R^{23}$, $N(R^{20})C(NR^{20})NHR^{23}$, $NR^{20}SO_2R^{21}$, OR^{20}, $OCONR^{20}R^{23}$, $OCONR^{20}SO_2R^{21}$, $OCONR^{20}R^{23}$, CN, CO_2R^{20}, $CONR^{20}R^{23}$, $CONR^{20}SO_2R^{21}$ and COR^{20};

R_3 is a halogen, hydroxyl, thio, alkoxy, alkylthio, alkyl, $-NR_4R_5$ or a component having the formula:



where m=1-3, n=1-3, o=1,3, y=carbonyl, $-NR_4R_5$, hydroxyl, thiol, alkoxy, alkylthiol;

R_4 and R_5 are each independently hydrogen, OR_{20}, $NR_{20}R_{23}$, or a hydrocarbon selected from the group including alkyl, acyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkenyl,and alkynyl, each having one to 20 carbon atoms, which alkyl, acyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkenyl,and alkynyl,are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, aryl, heteroaryl, heterocyclyl, R^{22}, SR^{20}, $S(O)R^{21}$, SO_2R^{21}, $SO_2NR^{20}R^{23}$, $SO_2NR^{20}COR^{21}$, $SO_2NR^{20}CONR^{20}R^{23}$, $SO_2NR^{20}CO_2R^{21}$, $NR^{20}R^{23}$, $NR^{20}COR^{21}$, $NR^{20}CO_2R^{21}$, $NR^{20}CONR^{20}R^{23}$,

$N(R^{20})C(NR^{20})NHR^{23}$, $NR^{20}SO_2R^{21}$, OR^{20}, $OCONR^{20}R^{23}$, $OCONR^{20}SO_2R^{21}$, $OCONR^{20}R^{23}$, CN, CO_2R^{20}, $CONR^{20}R^{23}$, $CONR^{20}SO_2R^{21}$ and COR^{20}; with the proviso that when Y is carbonyl, Y and R'_4 together may be a single oxygen atom, R_4" and R_5" together may be a single oxygen atom, R_4"' and R_5"' may together be a single oxygen atom, and wherein when R_3 is 2-hydroxyethylamino and R_2 is methyl, R_1'-X is not amino, 3-methyl-2-butenylamino, benzylamino, or m-hydroxybenzylamino, when R_3 is not 2-hydroxyethylamino, when R_2 is isopropyl, R_1'-X is not benzylamino, m-hydroxybenzylamino, or 3-methylbutylamino, when R_3 is 2-hydroxyethylamino and R_2 is 2-hydroxyethyl, R_1'-X is not benzylamino and when R_3 is selected from the group consisting of 2-methyl-2-hydroxypropylamino, and 2-dimethylaminoethylamino, and when R_2 is methyl, then R_1'-X is not benzylamino;

R^{20} is a member selected from the group consisting of H, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl, and heteroaryl, which alkyl, alkenyl, alkynyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from halo, alkyl, mono- or dialkylamino, alkyl or aryl or heteroaryl amide, CN, O-C_{1-6} alkyl, CF_3, aryl, and heteroaryl;

R^{21} is a member selected from the group consisting of C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl, and heteroaryl, which alkyl, alkenyl, alkynyl, aryl, heterocyclyl, and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from the group of halo, heterocyclyl, aryl, heteroaryl, CF_3, CN, OR^{20}, SR^{20}, $N(R^{20})_2$, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, $SO_2NR^{20}COR^{22}$, $SO_2NR^{20}CO_2R^{22}$, $SO_2NR^{20}CON(R^{20})_2$, $N(R^{20})_2$ $NR^{20}COR^{22}$, $NR^{20}CO_2R^{22}$, $NR^{20}CON(R^{20})_2$, $NR^{20}C(NR^{20})NHR^{23}$, COR^{20}, CO_2R^{20}, $CON(R^{20})_2$, $CONR^{20}SO_2R^{22}$, $NR^{20}SO_2R^{22}$, $SO_2NR^{20}CO_2R^{22}$, OR^{20}, $OCONR^{20}SO_2R^{22}$, $OC(O)R^{20}$, $C(O)OCH_2OC(O)R^{20}$, and $OCON(R^{20})_2$, and each optional heteroaryl, aryl, and heterocyclyl

substituent is optionally substituted with halo, alkyl, CF_3, amino, mono- or di- alkylamino, alkyl or aryl or heteroaryl amide, $NCOR^{22}$, $NR^{20}SO_2R^{22}$, COR^{20}, CO_2R^{20}, $CON(R^{20})_2$, $NR^{20}CON(R^{20})_2$, $OC(O)R^{20}$, $OC(O)N(R^{20})_2$, SR^{20}, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, CN, or OR^{20};

R^{22} is a member selected from the group consisting of C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl, and heteroaryl, which alkyl, alkenyl, alkynyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from halo, alkyl, mono- or dialkylamino, alkyl or aryl or heteroaryl amide, CN, O-C_{1-6} alkyl, CF_3, aryl, and heteroaryl; and

R^{23} is R^{21} or H.

2. A 2,6,9-trisubstituted purine composition of claim 1 wherein:

R'_1 is a alkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkenyl,and alkynyl, each having one to 20 carbon atoms, which alkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkenyl,and alkynyl,are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, CF_3, aryl, heteroaryl, heterocyclyl, R^{22}, SR^{20}, $S(O)R^{21}$, SO_2R^{21}, $SO_2NR^{20}R^{23}$, $NR^{20}R^{23}$, $NR^{20}COR^{21}$, $NR^{20}CO_2R^{21}$, $NR^{20}CONR^{20}R^{23}$, $NR^{20}SO_2R^{21}$, OR^{20}, CN, CO_2R^{20}, $CONR^{20}R^{23}$, and COR^{20};

R_2 is a hydrogen or hydrocarbon selected from the group substituted alkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkenyl,and alkynyl, each having one to 20 carbon atoms, which alkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkenyl,and alkynyl,are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, aryl, heteroaryl, heterocyclyl, R^{22}, SR^{20}, $S(O)R^{21}$, SO_2R^{21}, $SO_2NR^{20}R^{23}$, $NR^{20}R^{23}$, $NR^{20}COR^{21}$, $NR^{20}CO_2R^{21}$, $NR^{20}CONR^{20}R^{23}$, $NR^{20}SO_2R^{21}$, OR^{20}, CN, CO_2R^{20}, $CONR^{20}R^{23}$, and COR^{20};

R_4 and R_5 are each independently hydrogen, OR_{20}, $NR_{20}R_{23}$, or a hydrocarbon selected from the group including alkyl, acyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkenyl,and alkynyl, each having one to 20 carbon atoms, which alkyl, acyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkenyl,and alkynyl,are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, aryl, heteroaryl, heterocyclyl, R^{22}, SR^{20}, $S(O)R^{21}$, SO_2R^{21}, $SO_2NR^{20}R^{23}$, $NR^{20}R^{23}$, $NR^{20}COR^{21}$, $NR^{20}CO_2R^{21}$, $NR^{20}CONR^{20}R^{23}$, $NR^{20}SO_2R^{21}$, OR^{20}, CN, CO_2R^{20}, $CONR^{20}R^{23}$, and COR^{20};

R^{20} is a member selected from the group consisting of H, C_{1-8}alkyl, C_{2-8} alkenyl, C_{2-15} heterocyclyl, aryl, and heteroaryl, which alkyl, alkenyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from halo, alkyl, mono- or dialkylamino, alkyl or aryl or heteroaryl amide, CN, O-C_{1-6} alkyl, CF_3, aryl, and heteroaryl;

R^{21} is a member selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, heterocyclyl, aryl, and heteroaryl, which alkyl, alkenyl, aryl, heterocyclyl, and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from the group of halo, heterocyclyl, aryl, heteroaryl, CF_3, CN, OR^{20}, SR^{20}, $N(R^{20})_2$, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, $SO_2NR^{20}COR^{22}$, $SO_2NR^{20}CO_2R^{22}$, $SO_2NR^{20}CON(R^{20})_2$, $N(R^{20})_2$ $NR^{20}COR^{22}$, $NR^{20}CO_2R^{22}$, $NR^{20}CON(R^{20})_2$, $NR^{20}C(NR^{20})NHR^{23}$, COR^{20}, CO_2R^{20}, $CON(R^{20})_2$, $CONR^{20}SO_2R^{22}$, $NR^{20}SO_2R^{22}$, $SO_2NR^{20}CO_2R^{22}$, OR^{20}, $OCONR^{20}SO_2R^{22}$, $OC(O)R^{20}$, $C(O)OCH_2OC(O)R^{20}$, and $OCON(R^{20})_2$, and each optional heteroaryl, aryl, and heterocyclyl substituent is optionally substituted with halo, alkyl, CF_3, amino, mono- or di- alkylamino, alkyl or aryl or heteroaryl amide, $NCOR^{22}$, $NR^{20}SO_2R^{22}$, COR^{20}, CO_2R^{20}, $CON(R^{20})_2$, $NR^{20}CON(R^{20})_2$, $OC(O)R^{20}$, $OC(O)N(R^{20})_2$, SR^{20}, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, CN, or OR^{20}; and

R^{22} is a member selected from the group consisting of C_{1-8} alkyl, C_{2-8}alkenyl, heterocyclyl, aryl, and heteroaryl, which alkyl, alkenyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from halo, alkyl, mono- or dialkylamino, alkyl or aryl or heteroaryl amide, CN, O-C_{1-6} alkyl, CF_3, aryl, and heteroaryl.

3. A 2,6,9-trisubstituted purine composition of claim 1 wherein:

R'_1 is alkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkenyl,and alkynyl, each having one to 20 carbon atoms, which alkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkenyl,and alkynyl,are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, CF_3, aryl, heteroaryl, heterocyclyl, R^{22}, SR^{20}, $S(O)R^{21}$, SO_2R^{21}, $SO_2NR^{20}R^{23}$, $NR^{20}R^{23}$, $NR^{20}COR^{21}$, $NR^{20}CO_2R^{21}$, $NR^{20}SO_2R^{21}$, OR^{20}, CN, CO_2R^{20}, $CONR^{20}R^{23}$, and COR^{20};

R_2 is a hydrogen or hydrocarbon selected from the group including alkyl, heterocyclyl, and aryl, each having one to 10 carbon atoms, which alkyl, heterocyclyl, aryl,are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, aryl, heteroaryl, heterocyclyl, R^{22}, SR^{20}, $S(O)R^{21}$, SO_2R^{21}, $SO_2NR^{20}R^{23}$, $NR^{20}R^{23}$, $NR^{20}COR^{21}$, $NR^{20}CO_2R^{21}$, $NR^{20}SO_2R^{21}$, OR^{20}, CN, CO_2R^{20}, $CONR^{20}R^{23}$, and COR^{20};

R_4 and R_5 are each independently hydrogen, OR_{20}, $NR_{20}R_{23}$, or a hydrocarbon selected from the group including alkyl, acyl, heterocyclyl, aryl, heteroaryl, aralkyl, alkenyl,and alkynyl, each having one to 20 carbon atoms, which alkyl, acyl, heterocyclyl, aryl, heteroaryl, aralkyl, alkenyl,and alkynyl,are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, aryl, heteroaryl, heterocyclyl, R^{22}, SR^{20}, $S(O)R^{21}$, SO_2R^{21}, $SO_2NR^{20}R^{23}$, $NR^{20}R^{23}$, $NR^{20}COR^{21}$, $NR^{20}CO_2R^{21}$, $NR^{20}SO_2R^{21}$, OR^{20}, CN, CO_2R^{20}, $CONR^{20}R^{23}$, and COR^{20};

R^{20} is a member selected from the group consisting of H, C_{1-8}alkyl, aryl, and heteroaryl, which alkyl, aryl, and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from halo, alkyl, mono- or dialkylamino, alkyl or aryl or heteroaryl amide, CN, O-C_{1-6} alkyl, CF_3;

R^{21} is a member selected from the group consisting of C_{1-8} alkyl, aryl, and heteroaryl, which alkyl, aryl, and heteroaryl are optionally substituted with 1 to 2 substituents independently selected from the group of halo, CF_3, CN, OR^{20}, SR^{20}, $N(R^{20})_2$, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, $NR^{20}CO_2R^{22}$, $NR^{20}CON(R^{20})_2$, COR^{20}, CO_2R^{20}, $CON(R^{20})_2$, $NR^{20}SO_2R^{22}$, OR^{20}; and

R^{22} is a member selected from the group consisting of C_{1-8} alkyl, aryl, and heteroaryl, which alkyl, aryl, and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from halo, alkyl, mono- or dialkylamino, alkyl or aryl or heteroaryl amide, CN, O-C_{1-6} alkyl, CF_3, aryl, and heteroaryl.

4. A 2,6,9-trisubstituted purine composition of claim 1 wherein:

R'_1 is a alkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkenyl,and alkynyl, each having one to 20 carbon atoms, which alkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkenyl,and alkynyl,are optionally with from 1 to 2 substituents independently selected from the group consisting of halo, CF_3,, aryl, R^{22}, SR^{20}, $S(O)R^{21}$, SO_2R^{21}, $SO_2NR^{20}R^{23}$, $NR^{20}R^{23}$, $NR^{20}COR^{21}$, $NR^{20}CO_2R^{21}$, $NR^{20}SO_2R^{21}$, OR^{20}, CN, CO_2R^{20}, and $CONR^{20}R^{23}$;

R_2 is a hydrogen or hydrocarbon selected from the group alkyl, heterocyclyl, and aryl, each having one to 10 carbon atoms , which alkyl, heterocyclyl, aryl, are optionally substituted with from 1 to 2 substituents independently selected from the group consisting of

halo, aryl, heteroaryl, heterocyclyl, R^{22}, SR^{20}, $S(O)R^{21}$, SO_2R^{21}, $SO_2NR^{20}R^{23}$, $NR^{20}R^{23}$, $NR^{20}COR^{21}$, $NR^{20}CO_2R^{21}$, $NR^{20}SO_2R^{21}$, OR^{20}, CN, CO_2R^{20}, $CONR^{20}R^{23}$, and COR^{20};

R_4 and R_5 are each independently hydrogen, or a hydrocarbon selected from the group including alkyl, acyl, heterocyclyl, aryl, heteroaryl, aralkyl, alkenyl,and alkynyl, each having one to 20 carbon atoms, which alkyl, acyl, heterocyclyl, aryl, heteroaryl, aralkyl, alkenyl,and alkynyl,are optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, aryl, R^{22}, SR^{20}, $S(O)R^{21}$, SO_2R^{21}, $SO_2NR^{20}R^{23}$, $NR^{20}R^{23}$, $NR^{20}COR^{21}$, $NR^{20}CO_2R^{21}$, $NR^{20}SO_2R^{21}$, OR^{20}, CN, CO_2R^{20}, and $CONR^{20}R^{23}$;

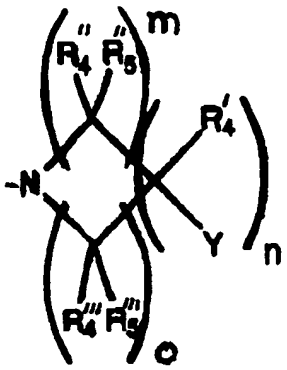
R^{20} is a member selected from the group consisting of H, C_{1-8}alkyl, aryl, and heteroaryl, which alkyl, aryl, and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from halo, alkyl, mono- or dialkylamino, alkyl or aryl or heteroaryl amide, CN, O-C_{1-6} alkyl, CF_3;

R^{21} is a member selected from the group consisting of C_{1-8} alkyl, aryl, and heteroaryl, which alkyl, aryl, and heteroaryl are optionally substituted with 1 to 2 substituents independently selected from the group of halo, CF_3, CN, OR^{20}, SR^{20}, $N(R^{20})_2$, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, $NR^{20}CO_2R^{22}$, $NR^{20}CON(R^{20})_2$, COR^{20}, CO_2R^{20}, $CON(R^{20})_2$, $NR^{20}SO_2R^{22}$, OR^{20}; and

R^{22} is a member selected from the group consisting of C_{1-8} alkyl, aryl, and heteroaryl, which alkyl, aryl, and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from halo, alkyl, mono- or dialkylamino, alkyl or aryl or heteroaryl amide, CN, O-C_{1-6} alkyl, CF_3, aryl, and heteroaryl.

5. The 2,6,9-trisubstituted purine composition of claim 1 wherein X=NH.

6. The 2,6,9-trisubstituted purine composition of claim 1 wherein R_3 is a component having the formula:



where m=1-3, n=1-3, o=1,3, y=carbonyl, $-NR_4R_5$, hydroxyl, thiol, alkoxy, alkylthiol with the provisos that when Y is carbonyl, Y and R'_4 together may be a single oxygen atom, R_4" and R_5" may together be a single oxygen atom, R_4"' and R_5"' may together be a single oxygen atom; and

R_4 and R_5 are each independently hydrogen, or a hydrocarbon selected from the group including alkyl, acyl, heterocyclyl, aryl, heteroaryl, aralkyl, alkenyl,and alkynyl, each having one to 20 carbon atoms, which alkyl, acyl, heterocyclyl, aryl, heteroaryl, aralkyl, alkenyl,and alkynyl,are optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, aryl, R^{22}, SR^{20}, $S(O)R^{21}$, SO_2R^{21}, $SO_2NR^{20}R^{23}$, $NR^{20}R^{23}$, $NR^{20}COR^{21}$, $NR^{20}CO_2R^{21}$, $NR^{20}SO_2R^{21}$, OR^{20}, CN, CO_2R^{20}, and $CONR^{20}R^{23}$.

7. The 2,6,9-trisubstituted purine composition of claim 3 wherein R_1' is selected from the group consisting of aralkyl and heteroarylalkyl.

8. The 2,6,9-trisubstituted purine composition of claim 7 wherein R_1' is selected from the group consisting of aralkyl, unsubstituted pyridylalkyl and substituted pyridylalkyl and wherein R_2 is selected from the group consisting of lower alkyl, substituted lower alkyl, and alkyl cycloalkyl.

9. A 2,6,9-trisubstituted purine composition of claim 5 wherein:

R'_1 is an aryl, heteroaryl, heterocyclyl, aralkyl, heteroarylalkyl, each having one to 20 carbon atoms, which aryl, heteroaryl, heterocyclyl, aralkyl, heteroarylalkyl, are optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, CF_3, aryl, R^{22}, SR^{20}, $S(O)R^{21}$, SO_2R^{21}, $SO_2NR^{20}R^{23}$, $NR^{20}R^{23}$, $NR^{20}COR^{21}$, $NR^{20}CO_2R^{21}$, $NR^{20}SO_2R^{21}$, OR^{20}, CN, CO_2R^{20}, and $CONR^{20}R^{23}$;

R_2 is a hydrogen or hydrocarbon selected from the group substituted lower alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl each having one to 10 carbon atoms wherein substitution includes optional substitution with from 1 to 2 substituents independently selected from the group consisting of halo, R^{22}, SR^{20}, $S(O)R^{21}$, SO_2R^{21}, $NR^{20}R^{23}$, OR^{20}, and CN;

R_4 and R_5 are each independently hydrogen, or a hydrocarbon selected from the group including alkyl, acyl, heterocyclyl, aryl, heteroaryl, aralkyl, alkenyl,and alkynyl, each having one to 20 carbon atoms, which alkyl, acyl, heterocyclyl, aryl, heteroaryl, aralkyl, alkenyl,and alkynyl,are optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, aryl, R^{22}, SR^{20}, $NR^{20}R^{23}$, $NR^{20}COR^{21}$, $NR^{20}CO_2R^{21}$, $NR^{20}SO_2R^{21}$, OR^{20}, CN, CO_2R^{20}, and $CONR^{20}R^{23}$;

R^{20} is a member selected from the group consisting of H, C_{1-8}alkyl, which alkyl is optionally substituted with 1 to 2 substituents independently selected from halo, alkyl, mono- or dialkylamino, alkyl or CN, O-C_{1-6} alkyl, CF_3;

R^{21} is a member selected from the group consisting of C_{1-8} alkyl, which alkyl is optionally substituted with 1 to 2 substituents independently selected from the group of halo, CF_3, CN, OR^{20}, SR^{20}, $N(R^{20})_2$; and

R^{22} is a member selected from the group consisting of C_{1-3}alkyl, aryl, heteroaryl which alkyl, aryl, and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from halo, alkyl, mono- or dialkylamino, alkyl or aryl, CN, O-C_{1-6} alkyl, CF_3.

10. The 2,6,9-trisubstituted purine composition of claim 3 wherein R_1' is selected from the group consisting of aryl, heterocyclyl, heteroaryl, substituted heteroaryl, and substituted aryl.

11. The 2,6,9-trisubstituted purine composition of claim 3 wherein R_1' is selected from the group consisting of aryl, unsubstituted pyridyl, substituted pyridyl, and substituted aryl, and R_2 is selected from the group consisting of alkyl, substituted alkyl.

12. The 2,6,9-trisubstituted purine composition of claim 2 wherein R_3 is $-NR_4R_5$ wherein R_4 and R_5 are each selected from the group consisting of hydrogen, alkyl, heterocyclyl, acyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkyl alkenyl, alkyl alkynyl, each having one to 20 carbon atoms, which alkyl, acyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl,are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, aryl, heteroaryl,heterocyclyl, R^{22}, SR^{20}, $S(O)R^{21}$, SO_2R^{21}, $SO_2NR^{20}R^{23}$, $NR^{20}R^{23}$, $NR^{20}COR^{21}$, $NR^{20}CO_2R^{21}$, $NR^{20}CONR^{20}R^{23}$, $NR^{20}SO_2R^{21}$, OR^{20}, CN, CO_2R^{20}, $CONR^{20}R^{23}$, and COR_{20}.

13. A 2,6,9-trisubstituted purine composition of claim 12 wherein:

R'$_1$ is an aryl, substituted aryl, each having 6 carbon atoms wherein substitution includes optional substitution with from 1 to 2 substituents independently selected from the group consisting of halo, CF_3, aryl, R^{22}, $NR^{20}R^{23}$, $NR^{20}COR^{21}$, OR^{20}, CN;

R_2 is a hydrogen or hydrocarbon selected from the group substituted lower alkyl, cycloalkyl, substituted cycloalkyl each having one to 6 carbon atoms wherein substitution includes optional substitution with from 1 to 2 substituents independently selected from the group consisting of halo, R^{22}, $NR^{20}R^{23}$, OR^{20};

R_4 and R_5 are each independently hydrogen, or a hydrocarbon selected from the group including alkyl, and heterocyclyl wherein each hydrocarbon has from 1 to 12 carbon atoms, which alkyl, and heterocyclyl are optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, R^{22}, SR^{20}, OR^{20} ,$NR^{20}R^{23}$, CN, CO_2R^{20}, and $CONR^{20}R^{23}$;

R^{20} is a member selected from the group consisting of H, C_{1-8}alkyl;

R^{21} is a member selected from the group consisting of C_{1-3} alkyl, which alkyl is optionally substituted with 1 to 2 substituents independently selected from the group of halo, CF_3, CN, OR^{20}, SR^{20}, $N(R^{20})_2$; and

R^{22} is a member selected from the group consisting of C_{1-3}alkyl, aryl, heteroaryl which alkyl, aryl, and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from halo, alkyl, mono- or dialkylamino, alkyl or aryl, CN, O-C_{1-6} alkyl, CF_3.

14. A 2,6,9-trisubstituted purine composition of claim 12 wherein:

R'_1 is an aryl, substituted aryl, each having 6 carbon atoms wherein substitution includes optional substitution with from 1 to 2 substituents independently selected from the group consisting of halo, CF_3, R^{22}, OR^{20}, CN;

R_2 is isopropyl;

R_4 and R_5 are each independently hydrogen, or a hydrocarbon selected from the group including alkyl, and heterocyclyl wherein each hydrocarbon has from 1 to 12 carbon atoms,

which alkyl, and heterocyclyl are optionally substituted with from 1 substituent independently selected from the group consisting of R^{22}, OR^{20}, $NR^{20}R^{23}$;

R^{20} is a member selected from the group consisting of H, C_{1-2}alkyl;

R^{21} is a member selected from the group consisting of C_{1-3} alkyl;

R^{22} is a member selected from the group consisting of C_{1-3}alkyl, aryl, which alkyl, aryl, are optionally substituted with 1 substituent independently selected from halo, alkyl, mono- or dialkylamino, CN, CF_3; and

R^{23} is R^{21} or H.

15. A 2,6,9-trisubstituted purine composition of claim 12 wherein:

R'_1 is an aralkyl, substituted aralkyl, each having 6-8 carbon atoms wherein substitution includes optional substitution with from 1 to 2 substituents independently selected from the group consisting of halo, CF_3, aryl, R^{22}, $NR^{20}R^{23}$, $NR^{20}COR^{21}$, OR^{20}, CN;

R_2 is a hydrogen or hydrocarbon selected from the group substituted alkyl, cycloalkyl, substituted cycloalkyl each having one to 6 carbon atoms wherein substitution includes optional substitution with from 1 substituent independently selected from the group consisting of halo, R^{22}, $NR^{20}R^{23}$, OR^{20};

R_4 and R_5 are each independently hydrogen, or a hydrocarbon selected from the group including alkyl and heterocyclyl wherein each hydrocarbon has from 1 to 12 carbon atoms, which alkyl and heterocyclyl are optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, R^{22}, SR^{20}, OR^{20} ,$NR^{20}R^{23}$, CN, CO_2R^{20}, and $CONR^{20}R^2$;

R^{20} is a member selected from the group consisting of H, C_{1-8}alkyl;

R^{21} is a member selected from the group consisting of C_{1-3} alkyl, which alkyl is optionally substituted with 1 to 2 substituents independently selected from the group of halo, CF_3, CN, OR^{20}, SR^{20}, $N(R^{20})_2$; and

R^{22} is a member selected from the group consisting of C_{1-3}alkyl, aryl, heteroaryl which alkyl, aryl, and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from halo, alkyl, mono- or dialkylamino, alkyl or aryl, CN, O-C_{1-6} alkyl, CF_3.

16. A 2,6,9-trisubstituted purine composition of claim 12 wherein:

R'_1 is $-CH_2-$phenyl wherein the phenyl ring is optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, CF_3, R^{22}, OR^{20}, CN;

R_2 is isopropyl;

R_4 and R_5 are each independently hydrogen, or a hydrocarbon selected from the group including alkyl, and heterocyclyl wherein each hydrocarbon has from 1 to 12 carbon atoms, which alkyl, and heterocyclyl are optionally substituted with from 1 to 2 substituents independently selected from the group consisting of R^{22}, OR^{20}, $NR^{20}R^{23}$;

R^{20} is a member selected from the group consisting of H, C_{1-2}alkyl;

R^{21} is a member selected from the group consisting of C_{1-3} alkyl;

R^{22} is a member selected from the group consisting of C_{1-3}alkyl, aryl, which alkyl, aryl, are optionally substituted with 1 substituent independently selected from halo, alkyl, mono- or dialkylamino, CN, CF_3; and

R^{23} is R^{21} or H.

17. The 2,6,9-trisubstituted purine composition of claim 12 wherein R_1' is selected from the group consisting of aralkyl, substituted pyridylalkyl, and unsubstituted pyridylalkyl;

R_2 is selected from the group consisting of alkyl, which alkyl is optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, R^{22}, $NR^{20}R^{23}$, OR^{20};

R_4 is a substituted alkyl having from 2 to 6 carbon atoms optionally substituted with from 1 to 3 substituents independently selected from the group consisting of R^{22}, OR^{20} , $NR^{20}R^{23}$;

R_5 is selected from the group consisting of hydrogen, alkyl, acyl, heterocyclyl, aryl, heteroaryl, aralkyl, each having one to 20 carbon atoms, which alkyl, acyl, heterocyclyl, aryl, heteroaryl, aralkyl,are optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, aryl, R^{22}, SR^{20}, $NR^{20}R^{23}$, $NR^{20}COR^{21}$, $NR^{20}CO_2R^{21}$, $NR^{20}SO_2R^{21}$, OR^{20}, CN, CO_2R^{20}, and $CONR^{20}R^{23}$;

R^{20} is a member selected from the group consisting of H, C_{1-2} alkyl;

R^{21} is a member selected from the group consisting of C_{1-3} alkyl;

R^{22} is a member selected from the group consisting of C_{1-3} alkyl, aryl, which alkyl, aryl, are optionally substituted with 1 substituent independently selected from halo, alkyl, mono- or dialkylamino, CN, CF_3; and

R^{23} is R^{21} or H.

18. The 2,6,9-trisubstituted purine composition of claim 12 wherein R_1' is selected from the group consisting of aryl, substituted aryl, pyridyl, and substituted pyridyl;

R_2 is selected from the group consisting of alkyl, which alkyl is optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, R^{22}, $NR^{20}R^{23}$, OR^{20};

R_4 is a substituted alkyl having from 2 to 6 carbon atoms optionally substituted with from 1 to 3 substituents independently selected from the group consisting of R^{22}, OR^{20} , $NR^{20}R^{23}$;

R_5 is selected from the group consisting of hydrogen, alkyl, acyl, heterocyclyl, aryl, heteroaryl, aralkyl, each having one to 20 carbon atoms, which alkyl, acyl, heterocyclyl, aryl, heteroaryl, aralkyl,are optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, aryl, R^{22}, SR^{20}, $NR^{20}R^{23}$, $NR^{20}COR^{21}$, $NR^{20}CO_2R^{21}$, $NR^{20}SO_2R^{21}$, OR^{20}, CN, CO_2R^{20}, and $CONR^{20}R^{23}$;

R^{20} is a member selected from the group consisting of H, C_{1-2} alkyl;

R^{21} is a member selected from the group consisting of C_{1-3} alkyl;

R^{22} is a member selected from the group consisting of C_{1-3} alkyl, aryl, which alkyl, aryl, are optionally substituted with 1 substituent independently selected from halo, alkyl, mono- or dialkylamino, CN, CF_3; and

R^{23} is R^{21} or H.

19. The 2,6,9-trisubstituted purine composition of claim 12 wherein R_1' is selected from the group consisting of aralkyl, pyridylalkyl, and substituted pyridylalkyl;

R_2 is selected from the group consisting of alkyl, which alkyl is optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, R^{22}, and OR^{20};

R_4 and R_5 are each a substituted alkyl having from 2 to 6 carbon atoms optionally substituted with from 1 substituent independently selected from the group consisting of R^{22}, $NR^{20}R^{23}$, and OR^{20};

R^{20} is a member selected from the group consisting of H, C_{1-2} alkyl;

R^{21} is a member selected from the group consisting of C_{1-3} alkyl;

R^{22} is a member selected from the group consisting of C_{1-3} alkyl; and

R^{23} is R^{21} or H.

20. The 2,6,9-trisubstituted purine composition of claim 12 wherein R_1' is CH_2 - aryl or CH_2 - substituted aryl, R_2 is lower alkyl or substituted lower alkyl, and R_4 and R_5 are each -CH_2 CH_2OH , -CHR'CH_2OH, or -CH_2 CHR'OH wherein R' is hydrogen or alkyl having from 1 to 6 carbon atoms.

21. The 2,6,9-trisubstituted purine composition of claim 12 wherein R_1' is CH_2-Aryl or CH_2-substituted aryl, R_2 is lower alkyl, and R_4 = H, and R_5 is -$CH_2CH_2NH_2$, CHR'CH_2NH_2, -CH_2CHR'NH_2 wherein R' is hydrogen or alkyl having from 1 to 6 carbon atoms.

22. The 2,6,9-trisubstituted purine composition of claim 21 wherein R_2 is isopropyl.

23. The 2,6,9-trisubstituted purine composition of claim 12 wherein R_1' is CH_2-Aryl or CH_2-substituted aryl, R_2 is lower alkyl, and R_4 = -CH_2CH_2OH R_5 is $CH_2CH_2NH_2$, or - CHR'CH_2NH_2, or - CH_2CHR'NH_2 wherein R' is hydrogen or alkyl having from 1 to 6 carbon atoms.

24. The 2,6,9-trisubstituted purine composition of claim 23 wherein R_2 is isopropyl.

25. The 2,6,9-trisubstituted purine composition of claim 20 wherein R_2 is isopropyl.

26. The 2,6,9-trisubstituted purine composition of claim 12 wherein R_1' is selected from the group consisting of aryl, substituted aryl, pyridyl, and substituted pyridyl, R_2 is

selected from the group consisting of lower alkyl, substituted lower alkyl, and alkyl cycloalkyl, and R_4 and R_5 are each a substituted lower alkyl having from 2 to 6 carbon atoms.

27. The 2,6,9-trisubstituted purine composition of claim 12 wherein R_1' is aryl or substituted aryl, R_2 is lower alkyl, or substituted lower alkyl, and R_4 and R_5 are each CH_2CH_2OH , -CHR'CH_2OH, or -CH_2CHR'OH wherein R' is hydrogen or alkyl having from 1 to 6 carbon atoms.

28. The 2,6,9-trisubstituted purine composition of claim 27 wherein R_2 is isopropyl.

29. The 2,6,9-trisubstituted purine composition of claim 12 wherein R_1' is benzyl substituted with a halogen, alkoxy, phenyl, pyridyl or nitro group, R_2 is isopropyl, and R_4 and R_5 are each -CH_2CH_2OH.

30. The 2,6,9-trisubstuted purine composition of claim 12 wherein R_1' is benzyl substituted with a halogen, alkoxy, phenyl, pyridyl or nitro group, R_2 is isopropyl, R_4 = H, and $R_5 = CH_2CH_2NH_2$.

31. The 2,6,9-trisubstuted purine composition of claim 12 wherein R_1' is benzyl substituted with a halogen, alkoxy, C_{1-3} alkyl, CF_3, phenyl, pyridyl or nitro group, R_2 is isopropyl, R_4 = H, and $R_5 = CH_2$CHR'NH_2 wherein R' is hydrogen or alkyl having from 1 to 6 carbon atoms.

32. The 2,6,9-trisubstuted purine composition of claim 12 wherein R_1' is benzyl substituted with a halogen, alkoxy, C_{1-3} alkyl, CF_3, phenyl, pyridyl or nitro group, R_2 is isopropyl, R_4 = H, and $R_5 = CH_2$CR'R'NH_2 wherein R' is hydrogen or alkyl having from 1 to 6 carbon atoms.

33. The 2,6,9-trisubstuted purine composition of claim 1 selected from the group consisting of 2-{(2-hydroxyethyl)[9-(methylethyl)-6-({[4-(trifluoromethyl)phenyl]methyl}amino)purin-2-yl]amino}ethan-1-ol, {((2S)oxolan-2-yl)methyl](6-{[(4-fluorophenyl)methyl]amino}-9-(methylethyl)purin-2-yl)amine, [((2R)oxolan-2-yl)methyl](6-{[(4-fluorophenyl)methyl]amino}-9-(methylethyl)purin-2-yl)amine, (2-aminoethyl)(6-{[3,5-dichlorophenyl)methyl]amino}-9-(methylethyl)purin-2-yl)amine, (2-aminoethyl)[6-({[4-chloro-3-(trifluoromethyl)phenyl]methyl}amino)-9-(methylethyl)purin-2-yl]amine, [-[(6-{[(4-chlorophenyl)methyl]amino}-9-(methylethyl)purin-2-yl)amino]-3-methylbutanamide, (2-amino-2-methylpropyl)(6-{[(4-chlorophenyl)methyl]amino}-9-(methylethyl)purin-2-yl)amine, 3-(2-[bis(2-hydroxyethyl)amino]-6-{[4-chlorophenyl)methyl]amino}purin-9-yl)butan-2-one, 2-[(6-{[(4-chlorophenyl)methyl]amino}-9-(methylethyl)purin-2-yl)amino]-3-methylbutan-1-ol, 4-[({2-[(2-aminoethyl)amino]-9-(methylethyl)purin-6-yl}amino)methyl]benzenesulfonamide, 2-[(2-hydroxyethyl)(6-{[(4-methoxyphenyl)methyl]amino}-9-(methylethyl)purin-2-yl)amino]ethan-1-ol, 2-((2-hydroxyethyl){9-(methylethyl)-6-[(4-phenylphenyl)amino]purin-2-yl}amino)ethan-1-ol, {2-[(2-amino-2-propyl)amino]-9-(methylethyl)purin-6-yl}[(4-hlorophenyl)methyl]amine, {2-[(2-aminoethyl)amino]-9-(methylethyl)purin-6-yl}[(4-chlorophenyl)methyl]amine, {2-[(2-aminopropyl)amino]-9-(methylethyl)purin-6-yl}[(4-chlorophenyl)methyl]amine and 2-[(2-aminoethyl)(6-{[(4-chlorophenyl)methyl]amino}-9-(methylethyl)purin-2-yl)amino]ethan-1-ol.

34. The 2,6,9-trisubstituted purine composition of claim 12 wherein R_1' is phenyl substituted with a halogen, alkoxy, phenyl, pryidyl or nitro group, R_2 is isopropyl, and R_4 and

R_5 are each $-CH_2CH_2OH$.

35. The 2,6,9-trisubstituted purine composition of claim 12 wherein R_1' is biphenylmethyl, R_2 is isopropyl, and R_4 and R_5 are each $-CH_2CH_2OH$.

36. The 2,6,9-trisubstituted purine composition of claim 12 wherein R_1' is selected from the group consisting of3-methylthiophenyl, 4-methylthiophenyl, 4-phenylbenzyl, 4-methoxybenzyl, 4-biphenyl, 3-methoxybenzyl, 4-(2-thienyl)benzyl, 4-(4-methyl)phenylbenzyl, 4-(4-trifluoromethyl)phenylbenzyl, 4-(4-nitrilo)phenylbenzyl, 4-(2-pyridinyl)benzyl, piperonyl, 3-methoxbenzyl, 4-chlorobenzyl, and 4-nitrobenzyl, R_2 is isopropyl, and R_4 and R_5 are both CH_2CH_2OH.

37. The 2,6,9-trisubstituted purine composition of claim 36 wherein R_1' is selected from the group of compounds consisting of 4-methoxybenzyl, 4-phenylbenzyl, 4-methoxybenzyl, 4-biphenyl, 3-methoxybenzyl, 4-(2-thienyl)benzyl, 4-(4-methyl)phenylbenzyl, 4-(4-trifluoromethyl)phenylbenzyl, 4-(4-nitrilo)phenylbenzyl, 4-(2-pyridinyl)benzyl, piperonyl, 3-thiomethoxphenyl, 4-thiomethoxyphenyl and 4-bromophenyl.

38. A cationic salt of the composition of claim 1.

39. An acid addition salt of the composition of claim 1.

40. A method for inhibiting cell proliferation in mammals comprising administering a therapeutically effective amount of the composition of claim 1 to the mammal.

41. The method of claim 40 wherein the therapeutically effective amount ranges from about 0.001 to about 100 mg/kg weight of the mammal.

42. The method of claim 40 wherein the composition is administered to a mammal suffering from a cell proliferation disorder selected from the group consisting of rheumatoid

arthritis, lupus, type I diabetes, multiple sclerosis, cancer, restenosis following ballon angioplasty or atherectomy, restenosis following vascular modifying surgical procedures, host graft disease, and gout.

43. The method of claim 42 wherein the cell proliferation disorder is restenosis.

44. The method of claim 42 wherein the cell proliferation is disorder cancer.

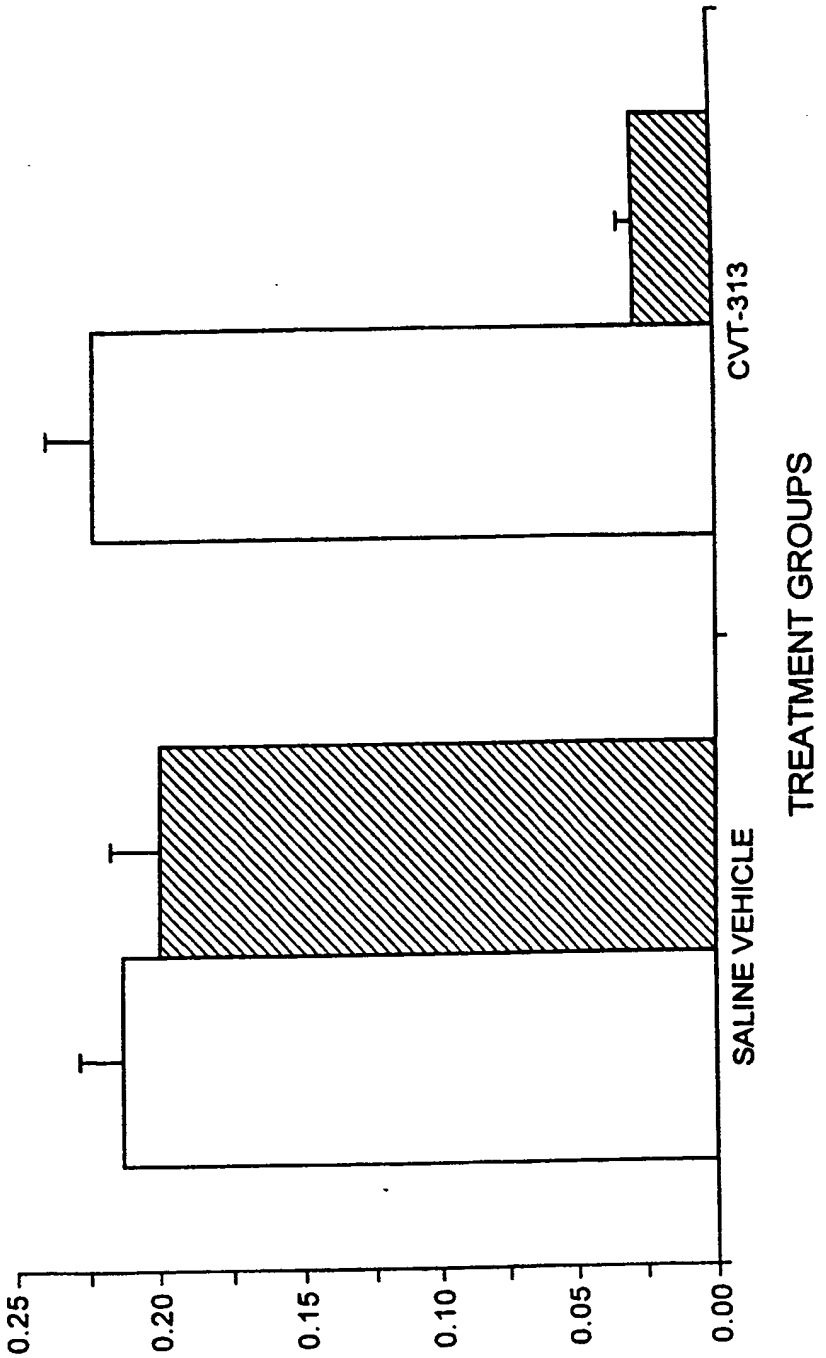
45. The method of claim 42 wherein the cell proliferation disorder is polycystic kidney disease.

46. The method of claim 42 wherein the mammal is a human.

47. A pharmaceutical composition of matter comprising the composition of claim 1 and one or more pharmaceutical excipients.

48. An antifungal agent useful for treating fungal infections in humans, and animals comprising the composition of claim 1.

49. The method of claim 42 wherein the cell proliferation disorder is selected from the group consisting of lymphoyd neoplasm, cancer of the colon, breast cancer, ovarian cancer, pancreatic cancer, and cancers derived from endothelial cells.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TREATMENT GROUPS

INTERNATIONAL SEARCH REPORT

In ational Application No
PCT/US 00/01407

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D473/40 C07D473/16 A61K31/52 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	WO 98 05335 A (CV THERAPEUTICS INC ;BLUM CHERI LYNN (US); LUM ROBERT T (US); MACK) 12 February 1998 (1998-02-12) the whole document	1-49
X	SCHOW S R ET AL: "Synthesis and Activity of 2,6,9-Trisubstituted Purines" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS,GB,OXFORD, vol. 7, no. 21, 1 January 1997 (1997-01-01), pages 2697-2702, XP002084930 ISSN: 0960-894X the whole document	1-49

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
31 May 2000	09/06/2000

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

In. .ational Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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